VOLUME 66 *December, 1952* NUMBER 6

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N.Y.

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THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY

Medical Section of National Tuberculosis Association

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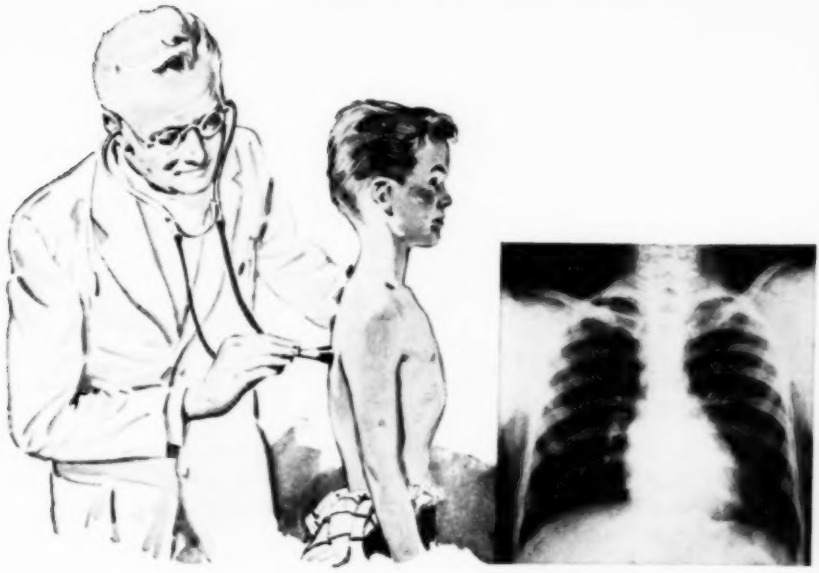

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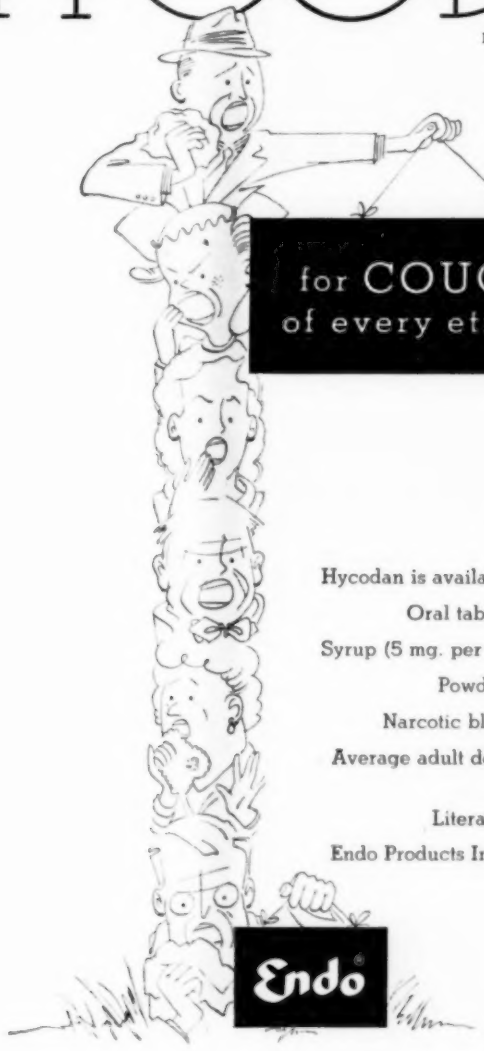

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L'action de l'isoniazide a été étudiée sur 14 cas de tuberculose miliaire aigue, dont quatre étaient également atteints de méningite. Onze autre cas de méningite tuberculeuse dont deux présentaient également une tuberculose miliaire, ont été traité par l'isoniazide administré en association ou postérieusement à la streptomycinothérapie.

THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 66 | *December 1952* | NUMBER 6

SURVIVAL OF TUBERCULOUS PATIENTS[1]

JULIUS KATZ

(Received for publication July 8, 1952)

Introduction

The practical use of survivorship data lies in their prognostic value. Although clinical studies serve to provide indices of the effects of stage of disease, age, sputum status, and other factors upon prognosis, study of tuberculosis mortality by the life-table method provides more accurate prognostic information. Since this information not only takes into consideration the clinical aspects of the disease but also deals in detail with the very important factor of time, the results obtained make studies of this type more comparable than is possible with the usual type of clinical report. This comparability of results is especially important at the present time, when so many new drugs for the treatment of tuberculosis are being developed. In studying the effectiveness of these drugs, survival data obtained among untreated patients may provide a standard with which the results obtained with the new agents may be compared.

It is the purpose of the present report to submit data regarding the survival of patients with pulmonary tuberculosis. The data were obtained in the course of a tuberculosis control program conducted since 1941 jointly by the New York State Departments of Mental Hygiene and of Health. All of the twenty-seven institutions of the former department, with a total population of approximately 100,000 patients, are included in this program.

Most studies of the survival of tuberculous patients do not present the complete natural history of tuberculosis because of the lack of accurate knowledge regarding the duration of the disease. Conclusions based upon the study of hospitalized patients or of those diagnosed in clinics or mass surveys suffer from this lack since neither the patient's history, the extent of disease, nor its roentgenographic appearance provides an accurate indication of the true age of the lesion. Since these studies must, however, begin at some arbitrarily chosen period and since the actual duration of the disease is usually unknown, the date of diagnosis may be used as the beginning of the period of observation. Tuberculous patients whose period of observation begins at this point comprise one of the two main groups of patients, the *old* cases of tuberculosis.

[1] From the Divison of Tuberculosis Control, New York State Department of Health, Albany, New York.

In order to obtain a more nearly complete time record of the disease as it progresses from its earliest stage, patients who have been under observation before they developed tuberculosis must also be studied so that the time of its earliest manifestation as shown by the roentgenogram may be established with reasonable accuracy. These patients comprise the other group, the *new* cases of tuberculosis.

For an adequate understanding of the usual dynamics of the disease, its evolution should be observed in patients who do not receive any form of specific therapy or who do not receive enough therapy to affect the course of the disease. Both *old* and *new* cases meet this requirement, since during most of the period of this study chemotherapy was not available and specific therapeutic measures such as pneumothorax and surgery were used only to a slight extent.

Plan of Study

A group of 1,851 mental patients who come within the definition of *new* cases have been studied. Each of these patients has had at least one chest roentgenogram negative for tuberculosis, therefore the duration of the disease can be determined with some degree of accuracy. Another group of patients, numbering 5,878, is included in this study as *old* cases of tuberculosis. The tuberculosis in these cases is of unknown duration since the disease was present at the time of the first chest roentgenogram.

In order to clarify the terms used in this report, the following definitions are offered:

A *new case* of tuberculosis is one in which the patient has had at least one negative chest roentgenogram while under observation. A case is considered *old* if the disease was present in the first roentgenogram taken of the patient. The difference between *new* and *old* cases consists, therefore, in the fact that in the former the approximate time of development of tuberculosis is known while, in the latter, the time of development of the disease is unknown.

The *time of diagnosis* is, in most instances, the time of the routine chest roentgenographic surveys of the institutions, made at intervals varying from two to five and one-half years, with an average interval between surveys of three and one-half years. Although the *new* disease may be from a few weeks to more than five years old, if it is assumed that the *new* cases were evenly distributed throughout the period between surveys, it may be estimated that the average case was twenty-one months old at the time of diagnosis. In some instances, where patients had roentgenograms because of the presence of symptoms or because of "spot" surveys of individual buildings within institutions, the cases may be of more recent origin.

As the term implies, *clinically significant cases* are those in which the patients are in need either of treatment or of relatively frequent medical supervision. These cases include those classified as active, quiescent, apparently arrested, or arrested according to the 1940 edition of the Diagnostic Standards of the National Tuberculosis Association, and as active or arrested in the 1950 edition. Cases not considered clinically significant were classified in the 1940 edition of Diagnostic Standards as apparently cured and, since 1950, as inactive.

The diagnoses of tuberculosis were made chiefly from the chest roentgenograms. In some cases sputum or gastric contents were known to contain tubercle bacilli. Continued observation of the patients, including additional films, tended to corroborate the diagnosis of tuberculosis.

Due to inadequate laboratory facilities and lack of personnel, examinations of sputum and gastric contents for tubercle bacilli were performed relatively infrequently; therefore no study could be made of the relationship between bacillary content of the sputum and survival of the patient.

As the control program was begun late in 1941, the maximum period of observation of any of these cases was approximately nine years, cases subsequently diagnosed having correspondingly shorter periods of observation. Consequently, the greatest number of cases had a one-year period of observation following diagnosis, with progressively smaller numbers having longer periods of study.

All deaths of tuberculous patients are included, whether due to tuberculosis or not. While deaths which occur during the first year after diagnosis, particularly among patients in the younger age group, are probably due mainly to tuberculosis, those which occur in the later years, especially among older patients, are more apt to be due to other causes. Thus, the periods of survival obtained in this study are probably underestimations of the actual survival of these patients from their tuberculous disease.

The life-table method was used in computing survival rates.

Results

NEW CASES

Distribution of New Cases

Two-thirds (65.3 per cent) of the 1,851 new cases developed among male patients and one-third (34.7 per cent) among females. For both sexes almost one-half of the cases of tuberculosis were minimal in extent at the time of diagnosis, approximately one-quarter were moderately advanced, while slightly more than one-quarter of the patients had far advanced disease (table 1).

Survivorship

Relationship to stage of disease: For the group as a whole, most of the deaths occurred during the first two years after diagnosis, following which the proportion of annual deaths occurred at a much lower rate so that, even eight years after the diagnosis of tuberculosis, almost half of the patients were still alive (table 2 and figure 1). The real effect of the impact of tuberculosis on mortality becomes evident, however, only when survival rates are studied in relation to the stage of disease at the time of diagnosis.

Among patients with minimal tuberculosis, most deaths occurred during the first two years, following which the proportion of deaths decreased so that, five years after diagnosis, more than 75 per cent of patients were still alive, and 70 per cent were still alive nine years after the diagnosis was made (table 2 and figure 1).

Patients with moderately advanced disease at the time of diagnosis showed a similar reaction to the disease in that fatalities were highest during the first two years, after which they continued at a much slower rate. Quantitatively, however, the effect of more extensive disease upon mortality became evident since five years after diagnosis fewer than half of the patients were alive (table 2 and figure 1).

The terrific toll of far advanced tuberculosis is apparent from table 2 and figure 1, which show a survival of less than 10 per cent after five years from the time of diagnosis, while only 5 per cent remained alive by the ninth year.

TABLE 1

DISTRIBUTION OF *NEW* CASES OF PULMONARY TUBERCULOSIS BY AGE, SEX, AND STAGE OF DISEASE AT TIME OF DIAGNOSIS

Age	TOTAL				MALES				FEMALES			
	Total	Min.	M.A.	F.A.	Total	Min.	M.A.	F.A.	Total	Min.	M.A.	F.A.
					Number of Cases							
Total*	1,851	849	441	561	1,208	568	286	354	643	281	155	207
Under 25	78	34	18	26	48	23	8	17	30	11	10	9
25–44	804	397	171	236	541	278	117	146	263	119	54	90
45–64	725	315	190	220	462	199	122	141	263	116	68	79
65 and over	237	100	59	78	152	66	36	50	85	34	23	28
					Per Cent of Cases							
Total	100.0	45.9	23.8	30.3	100.0	47.0	23.7	29.3	100.0	43.7	24.1	32.2
Under 25	100.0	43.5	23.1	33.3	100.0	47.9	16.7	35.4	100.0	36.7	33.3	30.0
25–44	100.0	49.4	21.3	29.3	100.0	51.4	21.6	27.0	100.0	45.2	20.5	34.2
45–64	100.0	43.4	26.2	30.3	100.0	43.1	26.4	30.5	100.0	44.1	25.9	30.0
65 and over	100.0	42.2	24.9	32.9	100.0	43.4	23.7	32.9	100.0	40.0	27.0	33.0

* Including age not stated
Min.—minimal
M.A.—moderately advanced
F.A.—far advanced

The close relationship between the extent of tuberculous disease in the lungs and survival is so well known as to need no comment. However, the data in table 2 show the rapidity with which tuberculosis can progress. As was mentioned above, the average duration of the tuberculous disease in these patients was probably approximately twenty-one months. Nevertheless, even within this relatively short period of time, only in fewer than half of the patients was the disease still in the minimal stage at the time of diagnosis, while in 24 per cent it had become moderately advanced, and in 30 per cent it was already far advanced.

On the other hand, the more optimistic observation can be made that, if the patient survives the first three years following diagnosis, his chances of living at least ten years are good, regardless of the stage of his disease (table 2 and figure 1).

TABLE 2

SURVIVAL RATES OF *New* CASES OF TUBERCULOSIS AMONG MENTAL PATIENTS, BOTH SEXES, BY STAGE OF DISEASE

PERIOD AFTER DIAGNOSIS	NUMBER AT BEGINNING OF PERIOD	NUMBER DYING DURING PERIOD	NUMBER WITHDRAWN DURING YEAR	SURVIVAL RATE		NUMBER AT BEGINNING OF PERIOD	NUMBER DYING DURING PERIOD	NUMBER WITHDRAWN DURING YEAR	SURVIVAL RATE	
				For Period	Cumulative				For Period	Cumulative
	I. All Stages					II. Minimal				
YEARS										
0–1	1,851	607	101	67.2	67.2	849	56	68	93.4	93.4
1–2	1,143	138	53	87.9	59.1	725	43	36	94.1	87.9
2–3	952	77	192	91.9	54.3	646	31	143	95.2	83.7
3–4	683	37	201	94.6	51.4	472	20	134	95.8	80.2
4–5	445	25	123	94.4	48.5	318	13	85	95.9	76.9
5–6	297	11	125	96.3	46.7	220	8	89	96.4	74.1
6–7	161	2	82	98.8	46.1	123	1	65	99.2	73.5
7–8	77	1	41	98.7	45.5	57	1	30	98.2	72.2
8–9	35	—	35	100.0	45.5	26	—	26	100.0	72.2
	III. Moderately Advanced					IV. Far Advanced				
0–1	441	120	25	72.8	72.8	361	431	8	23.2	23.2
1–2	296	44	15	85.1	62.0	122	51	2	58.2	13.5
2–3	237	25	38	89.5	55.5	69	21	11	69.6	9.4
3–4	174	10	50	94.3	52.3	37	7	8	81.1	7.6
4–5	105	8	29	92.4	48.3	22	4	9	81.8	6.2
5–6	68	3	33	95.6	46.1	9	—	3	100.0	6.2
6–7	32		15	100.0	46.1	6	1	2	83.3	5.2
7–8	17	—	8	100.0	46.1	3	—	3	100.0	5.2
8–9	9		9	100.0	46.1	—	—	—	—	—

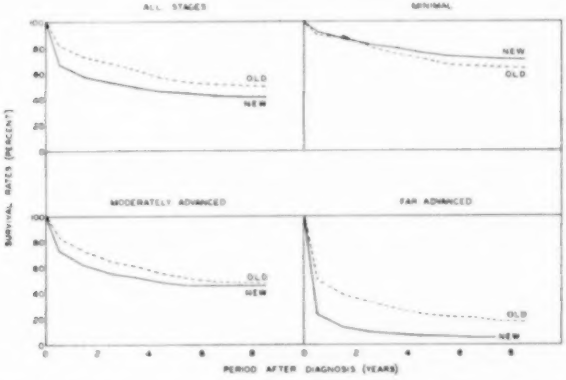

FIG. 1. Cumulative survival rates for *new* and *old* cases, both sexes, all ages, by stage of disease at time of diagnosis.

TABLE 2A

SURVIVAL RATES OF *New* CASES OF TUBERCULOSIS AMONG MENTAL PATIENTS, BOTH SEXES, BY AGE GROUPS

Cumulative Survival Rates

PERIOD AFTER DIAGNOSIS	MINIMAL AGE				MODERATELY ADVANCED AGE				FAR ADVANCED AGE			
	Under 25	25-44	45-64	65+	Under 25	25-44	45-64	65+	Under 25	25-44	45-64	65+
years												
0-1	100.0	92.9	95.2	87.0	55.6	71.9	74.2	74.6	38.5	25.9	20.0	19.2
1-2	89.7	88.7	89.4	81.8	43.3	61.6	65.7	56.0	16.5	13.8	12.7	13.7
2-3	85.7	86.0	84.4	74.0	43.3	56.9	59.6	40.5	16.5	9.8	9.8	4.6
3-4	85.7	82.6	79.9	72.5	43.3	54.6	55.0	37.8	16.5	8.8	7.5	1.5
4-5	85.7	80.5	76.4	65.4	31.6	49.6	51.6	37.8	16.5	6.6	7.5	0.0
5-6	85.7	79.7	72.6	59.1	31.6	49.6	48.3	28.4	16.5	6.6	7.5	—
6-7	85.7	79.7	70.9	59.1	31.6	49.6	48.3	28.4	16.5	6.6	3.8	—
7-8	85.7	79.7	67.9	59.1	—	49.6	48.3	—	16.5	6.6	—	—
8-9	85.7	79.7	67.9	59.1	—	49.6	48.3	—	—	—	—	—

TABLE 2B

SURVIVAL RATES OF *Old* CASES OF TUBERCULOSIS AMONG MENTAL PATIENTS, BOTH SEXES, BY STAGE OF DISEASE

PERIOD AFTER DIAGNOSIS	NUMBER AT BEGINNING OF PERIOD	NUMBER DYING DURING PERIOD	NUMBER WITHDRAWN DURING YEAR	SURVIVAL RATE		NUMBER AT BEGINNING OF PERIOD	NUMBER DYING DURING PERIOD	NUMBER WITHDRAWN DURING YEAR	SURVIVAL RATE	
				For Period	Cumulative				For Period	Cumulative
	I. All Stages					II. Minimal				
years										
0-1	5,878	1,092	623	81.4	81.4	2,779	233	230	91.6	91.6
1-2	4,163	418	207	93.0	73.3	2,316	154	82	93.4	85.6
2-3	3,538	273	223	92.3	67.7	2,080	117	100	94.4	80.8
3-4	3,042	219	117	92.8	62.8	1,863	103	62	94.5	76.4
4-5	2,706	174	98	93.6	58.8	1,698	97	54	94.3	72.0
5-6	2,434	138	289	94.3	55.4	1,547	71	176	95.4	68.7
6-7	2,007	87	329	95.7	53.0	1,300	43	221	96.7	66.4
7-8	1,591	34	688	97.9	51.9	1,036	12	424	98.8	65.6
8-9	869	9	860	99.0	51.4	600	6	594	99.0	64.9
	III. Moderately Advanced					IV. Far Advanced				
0-1	2,061	357	253	82.7	82.7	1,038	502	140	51.6	51.6
1-2	1,451	174	92	88.0	72.8	396	90	33	77.3	39.9
2-3	1,185	113	94	90.5	65.9	273	43	29	84.2	33.6
3-4	978	85	51	91.3	60.2	201	31	4	84.6	28.4
4-5	842	56	36	93.3	56.2	166	21	8	87.3	24.8
5-6	750	51	95	93.2	52.4	137	16	18	88.2	21.9
6-7	604	40	88	93.4	48.9	103	4	20	96.1	21.0
7-8	476	16	225	96.6	47.2	79	6	39	92.4	19.4
8-9	235	1	234	99.6	47.0	34	2	32	94.1	18.2

Relationship to age of patients: At each stage of the disease, older patients showed lower survival rates (table 2A and figure 2). Mortality was highest when the disease was newly acquired after sixty-five years of age. Among far advanced

TABLE 2C

SURVIVAL RATES OF *Old* CASES OF TUBERCULOSIS AMONG MENTAL PATIENTS, BOTH SEXES, BY AGE GROUPS

Cumulative Survival Rates

PERIOD AFTER DIAGNOSIS	MINIMAL AGE				MODERATELY ADVANCED AGE				FAR ADVANCED AGE			
	Under 25	25-44	45-64	65+	Under 25	25-44	45-64	65+	Under 25	25-44	45-64	65+
years												
0-1	92.9	95.6	94.4	79.0	89.4	90.0	84.3	71.6	50.0	53.9	53.8	45.1
1-2	87.0	91.4	89.3	67.9	67.9	80.8	76.6	58.0	44.5	41.3	41.4	35.0
2-3	81.9	87.6	85.4	59.7	53.4	73.9	71.7	48.2	37.1	35.6	36.2	26.4
3-4	79.6	83.8	81.6	52.7	53.4	70.4	65.5	41.1	37.1	28.7	32.2	20.5
4-5	79.6	80.3	78.5	44.0	53.4	68.5	61.9	34.3	37.1	27.4	27.4	16.5
5-6	79.6	77.8	75.5	38.5	53.4	66.0	57.6	29.9	37.1	26.7	23.5	13.2
6-7	79.6	76.9	72.1	36.7	45.8	63.6	54.4	25.2	37.1	26.7	22.2	12.5
7-8	79.6	76.7	71.3	35.3	45.8	62.4	52.7	23.3	37.1	25.6	20.6	10.7
8-9	79.6	76.3	70.4	34.8	45.8	62.4	52.3	23.3	—	25.6	18.3	10.7

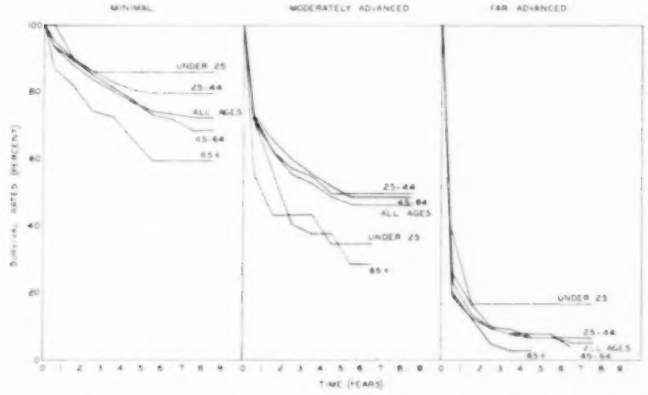

FIG. 2. Cumulative survival rates for *new* cases, both sexes, by stage of disease and age.

cases in this age group, the decrease in survival rates was so precipitous that after as short a time as two years few survived.

Relationship to sex of patients: One of the outstanding findings of this study was the marked similarity of survival rates among males and females. Whether the rates for the sexes were compared by stage of disease alone or by age and stage of disease, there was no appreciable difference in survival (figure 3). Due to the

similarity in survival, data for both sexes are considered together so that larger numbers may be obtained and more valid conclusions drawn from these figures.

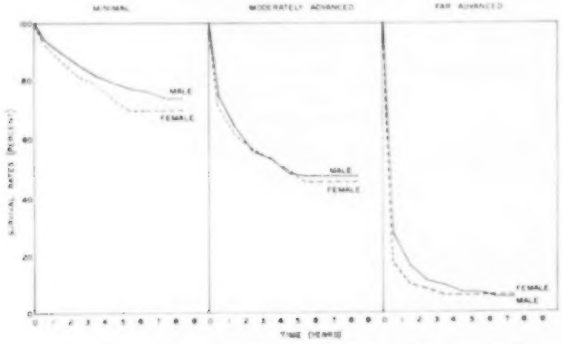

FIG. 3. Cumulative survival rates for *new* cases, all ages, by stage of disease and sex.

TABLE 3

DISTRIBUTION OF *Old* CASES OF PULMONARY TUBERCULOSIS BY AGE, SEX, AND STAGE OF DISEASE AT TIME OF DIAGNOSIS

AGE	TOTAL				MALES				FEMALES			
	Total	Min.	M.A.	F.A.	Total	Min.	M.A.	F.A.	Total	Min.	M.A.	F.A.
	Number of Cases											
Total	5,878	2,779	2,061	1,038	3,574	1,572	1,291	711	2,304	1,207	770	327
Under 25	174	85	47	42	94	49	23	22	80	36	24	20
25–44	1,796	911	568	317	1,135	558	371	206	661	353	197	111
45–64	2,555	1,215	907	433	1,555	665	575	315	1,000	550	332	118
65 and over	1,353	568	539	246	790	300	322	168	563	268	217	78
	Per Cent of Cases											
Total	100.0	47.3	35.1	17.6	100.0	44.0	36.1	19.9	100.0	52.4	33.4	14.2
Under 25	100.0	48.9	27.0	24.1	100.0	52.1	24.5	23.4	100.0	45.0	30.0	25.0
25–44	100.0	50.7	31.6	17.7	100.0	49.2	32.7	18.1	100.0	53.4	29.8	16.8
45–64	100.0	47.6	35.5	16.9	100.0	42.8	37.0	20.2	100.0	55.0	33.2	11.8
65 and over	100.0	42.0	39.8	18.2	100.0	38.0	40.8	21.3	100.0	47.6	38.5	13.9

Min.—minimal
M.A.—moderately advanced
F.A.—far advanced

OLD CASES

So far only those persons who developed tuberculosis during their period of hospitalization in mental institutions have been considered, the so-called new cases. In order that the survival data may present a more complete picture of

the effect of tuberculosis upon its victims, the group of old cases of tuberculosis must be studied. This group consists of those patients whose initial films showed the presence of clinically significant tuberculosis.

Distribution of Old Cases

Most of the old cases of tuberculosis were diagnosed among male patients, 60.8 per cent, with only 39.2 per cent among females (table 3). As was found among the new cases, in almost half of the old cases the tuberculosis was in the minimal stage at the time of diagnosis. However, proportionately more patients with old tuberculosis were in the moderately advanced stage, and fewer had far advanced disease (table 4). These differences may perhaps be explained by the relative instability of tuberculosis when it is far advanced, so that few patients remain in that stage for any considerable period of time, the disease tending

TABLE 4

DISTRIBUTION OF CASES OF PULMONARY TUBERCULOSIS BY AGE, SEX, AND STAGE OF DISEASE AT TIME OF DIAGNOSIS, FOR *New* AND *Old* CASES

Rates Per 100 Cases

ALL AGES PER CENT	BOTH SEXES				MALES				FEMALES			
	Total	Min.	M.A.	F.A.	Total	Min.	M.A.	F.A.	Total	Min.	M.A.	F.A.
Total *old* cases	100.0	47.3	35.1	17.6	100.0	44.0	36.1	19.9	100.0	52.4	33.4	14.2
Total *new* cases	100.0	45.9	23.8	30.3	100.0	47.0	23.7	29.3	100.0	43.7	24.1	32.2

Min.—minimal
M.A.—moderately advanced
F.A.—far advanced

either to recede and become less extensive or to progress and result in death of the patient.

Survivorship

Relationship to stage of disease: For the group as a whole, survival rates for old cases showed the same characteristics as those for the new cases; most deaths occurred during the first two years after diagnosis and there was a direct relationship between stage of disease and mortality.

Patients with minimal tuberculosis at the time of diagnosis had essentially the same chances of survival whether the disease was newly developed or old. The probability of survival of patients whose disease was moderately or far advanced was greater when the disease was old. For patients in these stages of the disease, the better prognosis for old cases during the first year after diagnosis was of statistical significance (table 2*B* and figure 1).

Relationship to age of patients: As in patients with newly developed tuberculosis, those with disease of longer duration also showed poorer prognoses in the older age groups so that, within each stage of disease, death rates were higher among older patients (table 2*C* and figure 4).

For patients with minimal tuberculosis, survival rates were essentially the same, age for age, among those with old as among those with new tuberculosis. Among patients with moderately advanced and far advanced disease the survival rates were higher for those with old tuberculosis.

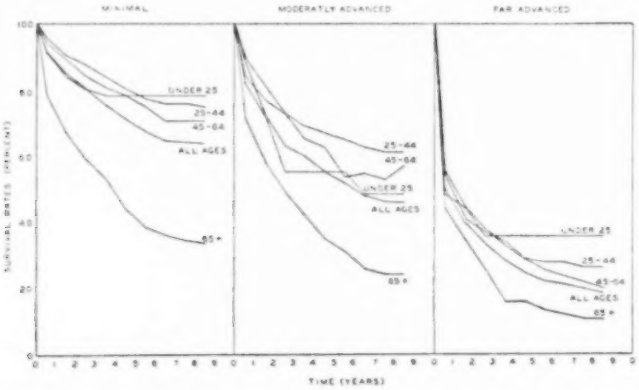

FIG. 4. Cumulative survival rates for *old* cases, both sexes, all ages, by stage of disease.

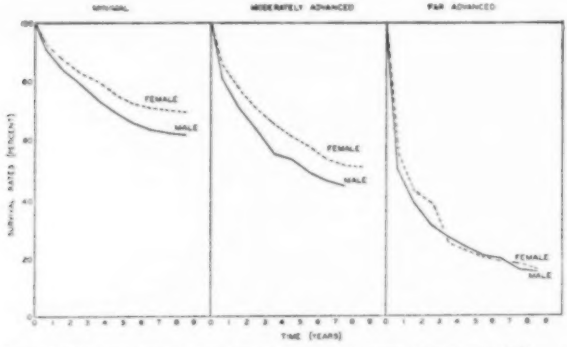

FIG. 5. Cumulative survival rates for *old* cases, all ages, by stage of disease and sex.

Relationship to sex of patients: Among old cases of tuberculosis as well as among newly developed ones, there was marked similarity of survival rates among male and female patients when compared by stage of disease alone or by age and stage of disease (figure 5).

DISCUSSION

The difference in survival rates between newly developed cases of tuberculosis and those of longer duration confirms a commonly held impression that during

the first year or so after the development of tuberculosis the mortality is higher than in subsequent years. Patients with new tuberculosis are less apt to have passed through this "sloughing-off" period than those with older disease; therefore differences in survival between the two groups result.

Among patients with minimal tuberculosis, whether the disease is new or old, the proportion dying from the disease during the first year is too small to make any significant difference in survival. Among those with moderately or far advanced disease, however, the elimination by death of many new cases during the first year is a more important factor, so that differences in survival rates are more pronounced. After the first two years, during which the disease has taken its heaviest toll of lives, the prognoses for new and old cases are similar.

Although old cases may be of any duration from a few weeks to many years, there is a greater mortality during the first year after diagnosis; in this respect the old cases resemble new ones. The explanation lies in the fact that the disease is not static and that the groups of patients with minimal, moderately advanced, and far advanced disease are not constant since patients are continually changing from one stage of disease to another. Within each group there are a number of patients whose disease is progressive and who contribute to the fatalities during each year of observation. It is this annual mortality which causes the similarity in the shape of the survivorship curves between old and new cases of tuberculosis (figure 1).

Since most known cases of tuberculosis fall into the *old* category, it is the group considered in this report as more suitable for comparison with reported studies. The prognosis for this group is considerably better during the first few years after diagnosis than for the group of new patients because of the selective factor of the higher mortality during the first year or two following the development of tuberculosis.

Regardless of whether the disease is new or old, survival data permit the following general prognostication. The mere fact that the disease is only minimal in extent at the time of diagnosis usually presages a good prognosis, while patients with moderately or far advanced disease have less favorable prognoses. This statement may seem self-evident, yet it has an important bearing upon the evaluation of the results of treatment. In view of the natural tendency toward healing of minimal tuberculosis, caution must be used in ascribing to a given form of treatment the good results associated with the therapy. In patients with moderately or far advanced disease, the results obtained are more likely to be due to the treatment. Even in these stages of disease, however, consideration must also be given to the age of the disease. If treatment is started during the first year after the diagnosis or the onset of the disease, when the natural tendency of the lesion is toward progression, improvement is more apt to be due to treatment than if therapy is begun later, when the tendency of the disease is toward regression.

The higher mortality among older patients is of importance in view of the increase in the age at which tuberculosis is being reported at present as compared with past years. Since no attempt has been made to determine the actual cause

of death of these patients, all deaths of tuberculous patients were included in this study even though many patients had other conditions which probably contributed to the death toll. This is particularly true of older patients, among whom degenerative diseases of the cardiovascular and renal systems and organic disease of the central nervous system are frequent.

The marked similarity in survival rates between males and females was unexpected. In view of the higher mortality rates among males, it was expected, a priori, that survival rates among males in this group would also be lower. Tattersall (1), in his report on "sputum-positive" dispensary patients, states that the outlook for males and females over twenty years of age is the same, while females below twenty have a poorer prognosis. He quotes Holst, Nicolaysen, and Ustvedt that "the difference in outlook for the two sexes is negligible." He also cites Cox in England, Backer in Norway, Lindhart in Denmark, and Berg in Sweden to the same effect.

There is one question which must be answered to determine whether conclusions based upon the data presented in this report are applicable to mental patients only or may be applied to other tuberculous patients. Does the fact that the information is obtained from mental patients, among whom the prevalence, incidence, and mortality from tuberculosis are much higher than in the general population, invalidate its applicability to tuberculous patients in general?

The best way to answer this question is to compare the results obtained among mental patients with similar studies among sane tuberculous patients. If the results obtained in both groups of patients are similar, it may be concluded that the fundamental reaction of mental patients to tuberculosis is similar to that of sane patients. Unfortunately, the literature on survival of tuberculosis patients is scanty, most reported studies being based upon the follow-up of patients after discharge from sanatoriums or of "sputum-positive" cases. Since the disease among patients in these categories is obviously of some duration, they will be compared with the old cases studied in this report.

Figure 6 shows survival rates for mental patients compared with several groups reported in the literature. It will be noted that survival rates among tuberculous mental patients fall between those reported by Hilleboe (2), obtained among patients discharged from sanatoriums in Minnesota, and those of Berg, Tattersall (1), and Thompson (3) among "sputum-positive" dispensary cases.

Hilleboe's cases are probably of longer duration than those among mental patients since the period of observation in his study begins at the time of discharge from the sanatorium rather than at the time of diagnosis of the disease, so that a greater amount of time has elapsed during which the "sloughing-off" of many patients with advanced disease has occurred. His patients are, therefore, a more select group, with a better prognosis than the tuberculous mental patients, even if the effect of their hospitalization upon the ultimate prognosis is disregarded.

The higher fatality rates found by Tattersall, Berg, and Thompson may also be explained by differences in selection of patients. The presence of tubercle bacilli in the sputum, especially when (as indicated by Tattersall) the sputum is

positive on smear, suggests that most patients had advanced disease. This is borne out by the fact that, among 1,046 patients in Tattersall's series, only 12 per cent had minimal lesions, compared with 47 per cent among mental patients. His group of patients, as well as those of the writers he mentions in his paper, therefore, comprises a group with a poorer prognosis.

Hilleboe's patients represent a select group of tuberculous patients with good prognoses, while those of Tattersall, Berg, and Thompson represent patients at the opposite end of the prognostic scale, whose survival rates are low. The survival from tuberculosis of large groups of patients from the general population, unselected because of age or clinical condition of the disease or any other factors, may be expected to fall between these extremes.

Since the patients reported in this study have survival rates well within the range between Hilleboe's and Tattersall's groups, it is believed that the survival

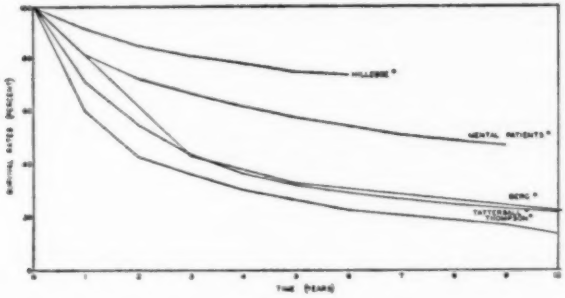

FIG. 6. Comparative survival rates.

* *See* text for references.

rates obtained do not deviate materially from what may be expected of a similar group of mentally sound tuberculous patients. The similarity in survival of male and female patients, found among insane as well as sane tuberculous patients, is additional evidence that the survival rates obtained among mental patients are in no way specific for these patients. Further, since these mental patients are not selected according to any of the characteristics of tuberculous disease, the absence of knowledge of their sputum status is no drawback because they may present more accurately a cross section of tuberculosis as it affects large groups of individuals, among whom the sputum status may vary from Gaffky 10 to negative for tubercle bacilli on animal inoculation.

Regardless of whether the data obtained in this study are applicable to mentally sound tuberculous patients, however, information regarding the survival of tuberculous patients, because of its prognostic value, is important in providing a basis for the evaluation of the effects of treatment. If the length of life of these patients, unaffected by specific therapy, were known, this information would provide a standard with which the results of any form of treatment might be com-

pared quantitatively. While, admittedly, the prolongation of life is not the only aim of specific therapy, it is, nevertheless, the most important of the criteria of successful treatment.

Summary

In studying the survival of tuberculous patients, two groups are encountered. One consists of those who developed tuberculosis while under observation, *new* cases; the other, of patients whose disease was present at the time of the initial chest roentgenogram, *old* cases. The latter group is much larger and of more practical importance.

With the use of this classification, a study has been made of the outcome of 7,729 cases of tuberculosis in patients in mental hospitals. It is concluded that:

There is a higher mortality during the first year after diagnosis among the *new* than among the *old* cases.

The mortality from tuberculosis is directly related to the stage of disease.

There is no difference between the sexes in survival from tuberculosis.

Tuberculosis survival rates among mental patients are probably similar to those among sane tuberculous patients.

SUMARIO

Sobrevivencia de los Tuberculosos

Al estudiar la sobrevivencia de los tuberculosos, encuéntranse dos grupos. Comprende uno a los que manifestaron tuberculosis mientras estaban en observación, casos "nuevos"; el otro, enfermos en que la dolencia se hallaba presente al tomar la radiografía torácica inicial, casos "viejos". El último grupo es mucho mayor y reviste más importancia práctica.

La mortalidad es mayor durante el primer año consecutivo al diagnóstico entre los casos "nuevos" que entre los "viejos".

La mortalidad debida a tuberculosis guarda relación directa con el período de la enfermedad.

No existe diferencia entre ambos sexos en lo tocante a sobrevivencia en la tuberculosis.

Las tasas de sobrevivencia de la tuberculosis entre los psicópatas son probablemente semejantes a las observadas en tuberculosos cuerdos.

RESUME

Survie des malades tuberculeux

En étudiant la survie des tuberculeux, deux groupes sont rencontrés. L'un se compose de ceux chez lesquels la tuberculose s'est développée pendant qu'ils étaient en observation, les "nouveaux" cas; l'autre se compose de malades dont la maladie existe au moment du radiogramme initial du poumon, les "vieux" cas. Ce dernier groupe est beaucoup plus grand et d'une importance pratique plus grande.

Pendant la première année qui suit le diagnostic, la mortalité est plus élevée parmi les nouveaux que parmi les vieux cas.

La mortalité par tuberculose est directement liée au stage de l'affection.

Il n'y a pas de différence entre les sexes dans la survie des malades atteints de tuberculose.

Dans la tuberculose, les taux de survie chez les sujets atteints d'une maladie mentale sont probablement les mêmes que ceux trouvés chez les tuberculeux indemnes de maladie mentale.

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OBSERVATIONS ON THE PROGRESSION OF MINIMAL PULMONARY TUBERCULOSIS[1]

A Study Based on Findings in Army Rejectees

HERBERT R. EDWARDS, DAVID REISNER, AND MARJORIE BELLOWS

(Received for publication July 8, 1952)

INTRODUCTION

Within the classification of minimal pulmonary tuberculosis as defined by the National Tuberculosis Association (1), there are two distinct factors to be considered in interpreting the roentgenographic findings. One is the extent of involvement; the other is the presumed pathologic basis for the character of the shadow revealed. It is quite obvious that there must be some relation between the future behavior of a given lesion and its total volume as well as its pathologic characteristics.

If there is to be a better understanding of the significance of the minimal lesion, there is need for a study of a reasonably random sample of individuals with such lesions over a period of time sufficient to determine their subsequent behavior. Such a study should include a large enough number of persons so that a reasonable conclusion can be drawn on the basis of sound statistical procedures. Furthermore, to be practical, it must be possible to define in concise terms both the extent and the character of the roentgenographic findings so that they may be readily visualized by the clinician who interprets the film. As the changes observed in the roentgenogram at present seem to offer the one common denominator in the diagnosis in these cases, it is desirable that, if possible, such simple criteria be set up as will enable the interpreter to make at least a broad classification of the lesions on the basis of the first film.

The army rejectee offered an unparalleled opportunity to study minimal lesions because the rejectees represented an unbiased selection of the male population between the ages of eighteen and thirty-nine. The part played by the New York City Department of Health in the follow-up program of Army rejectees has previously been reported (2, 3, 4).

MATERIAL FOR STUDY

During the period January 15, 1941, to February 28, 1943, the New York City induction stations referred 14,239 draftees to the New York City Health Depart-

[1] This study was conducted between 1943 and 1947. The authors at that time were connected with the New York City Department of Health: H. R. Edwards, Director of the Bureau of Tuberculosis; David Reisner, Medical Supervisor, Bureau of Tuberculosis; Marjorie Bellows, Director of the Central Statistical Division. The following members of the Department of Health staff rendered invaluable service to the study: Dr. Allan Hurst, Physician-in-charge, Central Chest Clinic; George Kerchner, Senior Statistician, the Statistical Division; Aaron Siegel, Supervisor, X-ray Technicians. Financial support for this study was obtained from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association. The major consultants represented the National Tuberculosis Association, the Public Health Service, The New York City Selective Service Board, and The Surgeon General's office of the United States Army.

ment for further roentgenographic examination and clinical study. Of the total referred, 1,363 failed to report for examination. Of the remaining 12,876, a total of 4,970 were excluded from the study for the following reasons:

Out-of-town residents	1,515
Local draft board not known	54
Receiving some form of collapse therapy	544
Diagnosed as negative	539
Nontuberculous chest conditions	2,218
Roentgenograms not located	100
Total	4,970

Thus, there remained a total of 7,906 draftees who were included in the initial phase of the study.

The 7,906 films taken at the time of referral to the Health Department were distributed for interpretation between two "readers" (who will be identified throughout as Dr. A. and Dr. B.) and were classified for: (*1*) diagnosis, (*2*) extent of lesion, and (*3*) presumed pathologic character of lesion.[2] The "readers" had no information about the cases other than the roentgenograms. Seventy-five per cent of the films were read independently by both "readers."

Letters were sent in August, 1944, to 7,199 rejectees, for whom addresses could be obtained through Selective Service, requesting them to appear at a special clinic for a follow-up roentgenographic examination. Of this group 4,581 reported. Roentgenograms taken elsewhere at approximately the same time were located for an additional 228 persons, making a total of 4,079 persons in which both initial and follow-up films were obtained.

Follow-up films were obtained later by various means for all but one of the persons with minimal lesions in sanatoriums, for all but two of those receiving pneumothorax treatments, and for all those reported as dead and in whom the death certificates indicated tuberculosis as the cause of death. As a result, the observed progression rates may be higher than if follow-up films had been obtained for the entire group.

Follow-up films were matched with the initial films and were distributed to the two "readers" without information concerning the diagnosis made on the original film. The second films were classified in the same manner as the original ones, i.e., according to diagnosis, extent and character of lesion. In addition, the dynamic status of the lesion was determined by comparing the two films in accordance with the following classifications:

A. Stationary (stable): No change noted in the extent or character of the lesion.

B. Regressive (retrogressive): A roentgenographically observed change in the extent and/or character of the lesion indicative of a favorable behavior. Regression may take place either by partial or by apparently complete absorption of the lesion, by organi-

[2] The classifications of character of lesions and definitions of terms adopted for this study were essentially the same as those outlined by Reisner and Downes in THE AMERICAN REVIEW OF TUBERCULOSIS, 1945, *51*, 393.

zation with fibrosis, by calcification, or by a combination of any of these modes of healing.

C. *Progressive*: Any increase in the extent of the lesion demonstrated in the roentgenogram regardless of the degree of progression. This may vary from a very slight to a marked increase in the area of involvement.

D. *Progression with cavity*: Development of demonstrable cavity either with or without increase in the total area of involvement.

Eighty-seven per cent of the paired films were read independently by both readers.

The group of roentgenograms initially selected for inclusion in the study had all previously been classified as showing some pathologic condition. Most of the initial films were standard 14- by 17-inch celluloid except for a small number of cases in which the initial roentgenogram was on sensitized paper. The follow-up roentgenograms were all on sensitized paper.

RESULTS OF STUDY

The original objective of the study was to determine whether it was possible to separate certain types of minimal lesions according to their relative risk of progression on the basis of their roentgenographic appearance. As this study was set up, it was limited to interpretation of a single roentgenogram without the aid of history or of physical or laboratory examination. The period of observation during which progression or regression could occur was, on the average, two years. This was a rather short period for adequate follow-up of the behavior of the lesion. The results, therefore, must be interpreted as a description of the rather immediate future behavior of minimal lesions.

It was the original intention to analyze progression rates by pooling the "readings" of the two physicians, each contributing half of the material. In view of the differences encountered, however, it seemed essential to keep the "readings" of each interpreter separate and analyze them as two separate groups of cases. In the discussion to follow, progression rates for Dr. A. are based on his "reading" of both the first and follow-up films for 1,664 cases, which he classified as minimal tuberculosis originally. Similarly, progression rates for Dr. B. are based on his "readings" of both the first and follow-up films on 2,185 cases, which he interpreted as minimal tuberculosis originally. More than half of the films in each group were also included in the other group.

Distribution of Lesions by Character and by Age and Color of Patient

The distribution by character of lesion in the cases of minimal tuberculosis "read" for progression by each interpreter may be seen in table 1. Comparing the distributions by character of lesion of the cases each interpreter had considered minimal, Dr. A. put a larger proportion of his cases in the two extreme groups than did Dr. B. While this may be partly the result of selection of cases classified by each of the two readers as minimal tuberculosis, it is of interest that, when identical groups of films were classified for extent of lesion by both, the findings were similar. The two interpreters appear to have had somewhat different patterns of classification for type of lesion.

The classification of minimal tuberculosis by age of patient and type of lesion for each interpreter is shown in table 2.

It should be recalled in interpreting these figures that at no time did the "readers" know the age of the patients. The films interpreted by Dr. A. as showing

TABLE 1

DISTRIBUTION OF MINIMAL LESIONS BY CHARACTER OF LESION

	NUMBER OF CASES		PERCENTAGE DISTRIBUTION	
	Dr. A.	Dr. B.	Dr. A.	Dr. B.
Total cases with minimal lesions	1,664	2,185	100.0	100.0
Exudative and exudative-productive*	300	316	18.0	14.5
Productive and fibro-productive	702	1,120	42.2	51.3
Fibrocalcific and calcified	662	749	39.8	34.3

* In analyzing the results of the study, minimal lesions classed as either exudative or exudative-productive have been grouped together. This was done partly because the number of persons with exudative lesions was extremely small and partly because a clear distinction between the two categories of lesions proved to be difficult to make.

TABLE 2

DISTRIBUTION OF CASES OF MINIMAL TUBERCULOSIS BY CHARACTER OF LESION AND AGE OF PATIENT

	Dr. A.			Dr. B.		
	Total	Under 25 years	25 years and over	Total	Under 25 years	25 years and over
Number of Cases						
Total minimal cases	1,664	232	1,432	2,185	338	1,847
Exudative and exudative-productive	300	81	219	316	81	235
Productive and fibro-productive	702	107	595	1,120	195	925
Fibrocalcific and calcified	662	44	618	749	62	687
Percentage Distribution by Character of Lesion						
Total	100.0	100.0	100.0	100.0	100.0	100.0
Exudative and exudative-productive	18.0	34.9	15.3	14.5	24.0	12.7
Productive and fibro-productive	42.2	46.1	41.6	51.3	57.7	50.1
Fibrocalcific and calcified	39.8	19.0	43.2	34.3	18.3	37.2

minimal tuberculosis included a slightly lower percentage (13.9 per cent) of persons less than twenty-five years of age than did those "read" by Dr. B. (15.5 per cent). Both "readers" found higher proportions of exudative and exudative-productive lesions in the younger age group than in the older one and a higher proportion of fibrocalcific and calcified lesions in the older age group.

However, the distribution of the cases in each of the two age groups by character of lesion was quite different for the two "readers." Dr. A. "read" 34.9 per

cent of the initial films of persons less than twenty-five years as showing exudative or exudative-productive lesions and 46.1 per cent as showing productive or fibro-productive lesions, whereas Dr. B.'s corresponding figures were 24.0 and 57.7 per cent, respectively. Both had approximately the same proportion with fibrocalcific or calcified lesions. In the older age group, Dr. A. classified more cases as exudative and exudative-productive and as fibrocalcific and calcified than did Dr. B. While the results of the interpretations of both "readers" showed that character of lesion was related to age, this relationship was more marked for Dr. A.

TABLE 3

DISTRIBUTION OF CASES OF MINIMAL TUBERCULOSIS BY CHARACTER OF LESIONS AND COLOR OF PATIENT

	Dr. A.			Dr. B.		
	Total	White	Non-White	Total	White	Non-White
Number of Cases						
Total minimal cases	1,664	1,501	163	2,185	1,942	243
Exudative and exudative-productive	300	249	51	316	276	40
Productive and fibro-productive	702	632	70	1,120	964	156
Fibrocalcific and calcified	662	620	42	749	702	47
Percentage Distribution by Character of Lesion						
Total minimal cases	100.0	100.0	100.0	100.0	100.0	100.0
Exudative and exudative-productive	18.0	16.8	31.3	14.5	14.2	16.5
Productive and fibro-productive	42.2	42.1	42.9	51.3	49.6	64.2
Fibrocalcific and calcified	39.8	41.3	25.8	34.3	26.1	19.3

The distribution by color of the patients whose films were viewed by each interpreter is shown in table 3. Again, it should be noted that the "readers" never knew the color of the patients whose films they were interpreting.

Of the films read by Dr. A. as showing minimal tuberculosis, 9.8 per cent were of non-white persons; of those read by Dr. B., 12.5 per cent were of non-white persons. The distributions by character of lesion among the whites and non-whites were, however, quite different for the two "readers." Dr. A. found that exudative and exudative-productive lesions occurred with twice the relative frequency among non-white persons as among whites; Dr. B. found that they occurred with nearly the same relative frequency in both color groups. Both "readers" found a color differential for the fibrocalcific and calcified lesions, there being a relatively higher frequency of this type of lesion among white persons. Dr. B., however, classified a higher proportion of both white and non-white persons as having productive and fibro-productive lesions than did Dr. A., the difference between the two "readings" being most pronounced among the non-white persons. The data presented in tables 2 and 3 would indicate that the two

"readers" had somewhat different subjective scales of classification according to character of lesion. Dr. A. not only had a narrower intermediate group and broader extreme groups, but his classification also had more pronounced age and color specificity.

TABLE 4

PROGRESSION RATES IN MINIMAL TUBERCULOSIS BY CHARACTER OF LESION

	Dr. A.			Dr. B.		
	Person-Years of Observation	Number of Cases Progressed	Rate per 100 Person-Years	Person-Years of Observation	Number of Cases Progressed	Rate per 100 Person-Years
Exudative and exudative-productive	594.00	76	12.8	631.00	64	10.1
Productive and fibro-productive	1,382.00	85	6.2	227.00	101	4.5
Fibrocalcific and calcified	1,320.50	18	1.4	1,519.25	17	1.1

TABLE 5

PROGRESSION RATES IN MINIMAL TUBERCULOSIS ACCORDING TO CHARACTER OF LESION AND AGE OF PATIENT

	Dr. A.			Dr. B.		
	Person-Years of Observation	Number of Cases Progressed	Rate per 100 Person-Years	Person-Years of Observation	Number of Cases Progressed	Rate per 100 Person-Years
Under 25 Years						
Exudative and exudative-productive	154.25	26	16.9	159.75	18	11.3
Productive and fibro-productive	212.75	25	11.8	378.75	31	8.2
Fibrocalcific and calcified	88.50	3	3.4	124.50	4	3.2
25 Years and Over						
Exudative and exudative-productive	439.75	50	11.4	471.25	31	6.6
Productive and fibro-productive	1,169.25	60	2.1	1,848.25	70	3.8
Fibrocalcific and calcified	1,232.00	15	1.2	1,394.75	13	0.9

Progression of Minimal Tuberculosis According to Character of Lesion

Dynamic status was determined by comparison of the first and follow-up roentgenograms without knowledge of how the first film had previously been interpreted.

In table 4 may be seen the *progression rates in minimal tuberculosis according to character of lesion* as rates per 100 person-years of observation.

While Dr. A.'s cases had slightly higher progression rates than Dr. B.'s for all types of lesions, the relative differences in rates for various types of lesions were

almost the same for both "readers." The progression rates per 100 person-years of observation for exudative and exudative-productive lesions were a little more than twice those for productive and fibro-productive lesions and more than nine times as high as the rates for fibrocalcific and calcified lesions.

Progression According to Character of Lesion and Age of Patient

Progression rates according to character of lesion and age of patients are shown in table 5. Although the progression rates for the cases interpreted by Dr. B. were consistently lower than for those interpreted by Dr. A., the relationships between age of patient and character of lesion were much the same. Progression

TABLE 6

PROGRESSION RATES IN MINIMAL TUBERCULOSIS SHOWING CHARACTER OF LESION AND COLOR OF PATIENT

	DR. A.			DR. B.		
	Person-Years of Observation	Number of Cases Progressed	Rate per 100 Person-Years	Person-Years of Observation	Number of Cases Progressed	Rate per 100 Person-Years
White						
Exudative and exudative-productive	499.25	63	12.6	558.50	52	9.3
Productive and fibro-productive	1,250.00	67	5.4	1,919.00	84	4.4
Fibrocalcific and calcified	1,237.50	16	1.3	1,424.00	16	1.1
Non-whites						
Exudative and exudative-productive	94.75	13	13.7	73.5	12	16.3
Productive and fibro-productive	132.00	18	13.6	308.0	17	5.5
Fibrocalcific and calcified	83.00	2	2.4	95.25	1	1.0

rates for all types of lesion were higher among persons less than twenty-five than for those twenty-five years and older. The age difference was less, however, for exudative and exudative-productive lesions than for the other two types of lesion. It is notable that both "readers" found higher progression rates for productive and fibro-productive lesions in persons less than twenty-five years of age than for exudative and exudative-productive lesions in persons twenty-five years and older. In other words, age of the patient as well as character of the lesion appears to be an important consideration in so far as risk of progression is concerned.

Progression According to Character of Lesion and Color of Patient

Although the numbers of non-white persons are very small, progression rates have been computed for whites and non-whites for all ages as shown in table 6.

It is difficult to interpret the rather wide differences in the findings of the two

"readers," but in general it appears that progression rates are higher for all types of lesions among non-whites than among white persons. The results obtained by one "reader" would indicate that there was little difference between the two color groups in the rate of progression of exudative and exudative-productive lesions, but that the progression rate for productive and fibro-productive lesions among non-white persons was markedly higher than among white persons. In fact, it was higher even than the rates for exudative-productive lesions among white persons. Nevertheless, this latter observation was not confirmed by the other "reader." Indeed, the only group in which he noted a markedly higher progression rate among non-white persons was in the exudative and exudative-productive group. The age distribution of the non-white groups of cases differed for the two "readers," Dr. B. having a higher proportion of cases of persons less than twenty-five years. This factor, however, does not account for the differences noted.

TABLE 7

STABILITY RATES IN MINIMAL TUBERCULOSIS BY CHARACTER OF LESION AND AGE OF PATIENT

Percentage of Cases Remaining Stable

	EXUDATIVE AND EXUDATIVE-PRODUCTIVE		PRODUCTIVE AND FIBRO-PRODUCTIVE		FIBRO-CALCIFIC AND CALCIFIED	
	Dr. A.	Dr. B.	Dr. A.	Dr. B.	Dr. A.	Dr. B.
White						
Under 25 years	15.5	37.7	58.4	71.5	87.5	89.7
25 years and over	40.5	63.8	82.3	89.4	95.3	97.3
Non-White						
Under 25 years	0.0	0.0	50.0	82.6	100.0	100.0
25 years and over	41.5	50.0	65.6	85.0	94.9	97.7

Stability of Minimal Lesions

The dynamic status of the lesion was classified as progressive, stable, or regressive. The three types of lesion in various age and color groups may be analyzed by comparing the percentages of lesions in each group that remained stable as shown in table 7.

The differences in actual percentages between the two "readers" were quite marked and Dr. B. classified a considerably larger proportion of cases as stable. Despite these differences, however, the results on a relative basis were similar. Exudative and exudative-productive lesions showed the least stability, and this type of lesion was more unstable among persons less than twenty-five years of age. Productive and fibro-productive lesions were more stable than the exudative and exudative-productive type and, again, there was an age differential, the lesions being less stable in the younger age group. This was the only group in which the number of non-white persons was large enough to justify comment. There appears to have been considerably less stability of exudative and exudative-productive lesions in non-whites than in white persons. Fibrocalcific and calcified

lesions were the most stable, with the highest percentage of stability in the group twenty-five years of age and over.

Mortality

The crude mortality rates among all cases of minimal tuberculosis were identical for the films read by the two interpreters, 2.3 per 1,000 person-years of observation. The numbers were too small for comparison of specific death rates by age and color for the various types of lesion. Death rates for the various types of lesion were also based on figures too small to measure reliably the mortality risk for each type, but they may be compared as shown in table 8.

Mortality was higher among persons with exudative and exudative-productive lesions than among those with productive and fibro-productive lesions. No deaths were recorded among persons with fibrocalcific and calcified lesions in either "reader's" group.

TABLE 8

DEATH RATES PER 1,000 PERSON-YEARS OF OBSERVATION IN MINIMAL TUBERCULOSIS BY CHARACTER OF LESION

	DR. A.			DR. B.		
	Person-Years of Observation	Number of Deaths	Rate per 1,000	Person-Years of Observation	Number of Deaths	Rate per 1,000
Exudative and exudative-productive	898.3	4	4.5	964.1	7	7.3
Productive and fibro-productive	2,251.3	8	3.6	3,356.8	8	2.4
Fibrocalcific and calcified	1,983.8	—	—	2,175.1	—	—

DISCUSSION

As indicated at the outset, the objective of this study was to determine the behavior of the minimal lesion of pulmonary tuberculosis detected in army selectees. In essence, this report deals with an attempt to demonstrate the extent to which the roentgenogram alone, especially a single film, may be used for the purpose stated. As was previously mentioned, the interpretation of the films and the classification of the lesions were made without knowledge of other data pertaining to the patient, even of such facts as age and color. It is necessary to stress this point since such a procedure, although it may be justified as a means of studying the value or limitations of a particular method of examination, would hardly be used in actual clinical practice.

This material did not meet the requirements for a long-range study of minimal tuberculosis since the period which elapsed between the dates of the initial and follow-up films amounted to only two years in the majority of cases. Furthermore, the dynamic status of the lesion was determined on the basis of comparison of the initial film with the final film, without taking into consideration changes that might have occurred during the intervening period. Although, in part of the material, roentgenograms taken at periodic intervals were available, they were

not utilized for the purpose of this study in order to ensure a uniform procedure for all cases. Because of lack of continuous follow-up, the actual behavior of the lesion during the whole period of observation could not be determined.

A point which became apparent during the initial phase of the study was the factor of variability in the interpretation of roentgenograms. It thus became obvious that there were two basic problems at issue instead of one as originally thought, i.e., first, the question concerning the feasibility of using a predetermined classification of the lesion on the basis of a single roentgenogram; second, the significance of the variability of roentgenographic interpretation in applying such a classification when used by more than one interpreter.[3]

The disagreement in classifying the character of the lesions appeared to be most pronounced in the differentiation between lesions of the exudative and exudative-productive group and those classified as productive and fibro-productive. The differences were considerably smaller in the fibrocalcific and calcified group.

Of the cases included in the exudative and exudative-productive group, the preponderant majority were classified as the mixed exudative-productive type. Only a very small number, approximately 2.0 per cent of the entire minimal group, was classed as predominantly exudative in character. The apparent difficulties in separating the exudative-productive lesions from those classified as productive or fibro-productive may be explained by the fact that, according to the definitions, these two groups of lesions have certain features in common, namely, the "hard" productive and fibrotic element. It would seem that a differentiation between intermediate types of lesion is more difficult and therefore more subject to individual variations than a distinction between extreme types of lesion, as the latter are likely to give a more characteristic roentgenographic appearance than the former.

Two points should be mentioned in connection with the variability in interpreting dynamic status of the lesion: first, the variable technical factors including the different roentgenographic media employed in the study. It is likely that in a certain number of cases a slight change noted by comparing two films may be considered by one "reader" as only an apparent change caused by technical factors, while to the other "reader" this finding may indicate a real change in the pathologic process.

The second point is the inability, on the basis of the available data, to determine the practical significance of the disagreement in classifying dynamic status of the lesion, especially with regard to progression. According to the accepted terminology, any increase in the area of involvement, irrespective of the degree, was to be considered as progression. From a clinical standpoint, it would have been most desirable to separate cases in which the disagreement was of serious nature, such as that between frank progression and no progression, from those cases in which the disagreement was of a less serious character, as "slight progression" designated by one interpreter and "no progression" by the other.

[3] The data on variability in film interpretation have been analyzed in detail and this phase of the study will be the subject of a separate publication.

Because of variations in classifying the lesion according to its extent, on the basis of the initial film, the material did not lend itself to an analysis from this point of view.

Although considerable variability was encountered in using the predetermined classification of minimal tuberculosis, the data indicate that there were consistent differences in the behavior of the lesion which appeared to be related to its character. When character of the lesion alone was considered without regard to such factors as age and color of the patient, lesions classed as exudative or exudative-productive showed a higher rate of instability, manifested as either progression or regression, than any of the other types. Lesions of the fibrocalcific and calcified types were stable in the preponderant majority of cases, while those classified as productive or fibro-productive occupied an intermediate position between the other two groups.

The differences in the behavior of the minimal lesions between those classed as exudative or exudative-productive and those of the productive or fibro-productive type observed in the present material were less striking than those found by Reisner and Downes (5) in a previous study. However, the material reported by Reisner and Downes is not quite comparable with the present study. In the former, the proportion of predominantly exudative lesions was much greater than in the present material, in which this type of lesion was represented by a very small number of cases. The majority of cases included in the exudative group were of the combined exudative-productive type.

The experience based on the material of the present study indicates that the overwhelming majority of minimal tuberculous lesions found in surveys of apparently healthy adults can be divided into two broad categories. One group would seem to comprise intermediate types of lesions which may be classified as either exudative-productive, productive, or fibro-productive; the other group consists of lesions of an apparently healed, fibrocalcific, or calcified type. The number of cases showing lesions of a predominantly exudative character, which may be assumed to be of recent origin, was extremely small. A further separation of lesions of the intermediate category into distinct types may prove to be quite difficult, especially if attempts are made to do this on the basis of a single roentgenogram.

In classifying minimal lesions found in mass surveys, it would seem preferable to separate such lesions into not more than three broad groups, as follows: two extreme types, one comprising the predominantly "soft," exudative form; the other, the "hard," stringy fibrotic and calcified types. A third group may include lesions not definitely classifiable into either one or the other of the preceding types and would represent an intermediate category of lesions.

Significant age differences in progression rates were observed between persons less than twenty-five and those twenty-five years of age or older. Higher progression rates were noted for all types of lesion in the younger age group although this difference was less pronounced for the exudative and exudative-productive lesions than for those classed as productive or fibrotic. The extent to which such differences in the behavior of the minimal lesion may be due to the age of the host or the degree to which they may be related to the relative recency of the lesion is

impossible to determine on the basis of the available data. The present findings concerning the relationship between character of lesion in minimal tuberculosis and the age of the patient are similar to the observations reported by Bobrowitz, Hurst, and Martin (6).

An accurate evaluation of the racial factor as it relates to the behavior of the minimal lesion is not possible on the basis of the available material. The number of cases in the non-white group was too small to permit a detailed analysis and comparison with the white group. On the whole, there was a greater tendency to progression and instability of all types of lesion in non-white persons than in white persons. This is in agreement with observations reported in other studies dealing with the behavior of minimal tuberculosis.

SUMMARY

A study of minimal lesions of chronic pulmonary tuberculosis was carried out in army selectees who had been rejected for military service because of abnormal findings in the preinduction chest roentgenogram. The principal objective of the study was an attempt to determine the extent to which the roentgenogram alone, without the aid of clinical and laboratory data, may be used as a guide in estimating the future behavior, and therefore the clinical significance, of minimal lesions detected in mass or group surveys. A classification of minimal tuberculous lesions based on their presumed pathologic character was used, and the lesions were grouped into the following three main categories: (*a*) exudative and exudative-productive; (*b*) productive and fibro-productive; (*c*) fibrocalcific and calcified. The behavior of the lesions, i.e., progression, regression, or stability, was determined by comparing the initial roentgenogram with the latest film made available for the purpose of the study.

Consistent differences in the behavior of minimal lesions which appeared to be related to their character were observed. Progression rates were highest in the group classed as exudative or exudative-productive and lowest in the fibrocalcific and calcified group. The reverse order was true for rates at which stability of the lesions was observed. In addition to character of the lesion, the age of the patient appeared to be of significance. Higher progression rates were observed among persons under the age of twenty-five than in those twenty-five years of age or over.

The limitations inherent in the objective of this study and in the procedures employed have been discussed. Because of the relatively short follow-up period of the cases and the fact that the analysis was limited solely to an evaluation of roentgenographic findings, it is not believed that this study meets the essential requirements of a more complete and long-term study of the clinical significance and prognosis of minimal tuberculosis.

SUMARIO

Observaciones acerca de la Progresión de la Tuberculosis Pulmonar Mínima: Estudio Basado en los Hallazgos en los Rechazados para el Ejército

Este estudio de las lesiones mínimas de la tuberculosis pulmonar crónica fué llevado a cabo en reclutas rechazados para servicio militar por virtud de hallazgos anómalos descubiertos en las radiografías torácicas tomadas antes del ingreso.

Fué objeto principal del estudio tratar de determinar hasta qué punto cabe usar las radiografías por sí solas, sin la ayuda de los datos clínicos y de laboratorio, como guía para apreciar el comportamiento futuro, y por ende la importancia clínica, de las lesiones mínimas descubiertas en las encuestas colectivas.

Se usó una clasificación de las lesiones tuberculosas mínimas, basada en su supuesta naturaleza patológica, dividiéndose el material disponible en los tres grandes grupos siguientes: (*a*) exudativo y exudativo-productivo, (*b*) productivo y fibro-productivo, (*c*) fibro-calcificado y calcificado.

El comportamiento de las lesiones, es decir, progresión, regresión o estabilidad, fué determinado comparando la radiografía inicial con la última disponible para los fines de este estudio.

Observáronse diferencias constantes en el comportamiento de las lesiones mínimas que parecían guardar relación con la naturaleza de las últimas. Los coeficientes de progresión alcanzarón su máximo en el grupo clasificado como exudativo o exudativo-productivo y su mínimo en el fibro-calcificado o calcificado. Sucedió lo contrario en lo relativo a estabilidad de las lesiones.

Además de la naturaleza de la lesión, la edad del enfermo parecía poseer importancia, observándose tasas más altas de progresión entre las personas de menos de veinticinco años que entre las de más edad.

Se discuten las limitaciones impuestas por el objeto de este estudio y por los procedimientos empleados. Debido al período relativamente breve de observación subsiguiente y al hecho de que el análisis se limitó exclusivamente a la valuación de los hallazgos radiográficos, parece que este estudio no acaba de cumplir los requisitos esenciales de un estudio más completo y a largo plazo de la significación clínica y del pronóstico de la tuberculosis mínima.

RESUME

Observations sur la progression de la tuberculose pulmonaire minimale: Etude fondée sur les lésions observées chez les réformés de l'armée

Une étude des lésions minimales de la tuberculose pulmonaire chronique a été effectuée chez des réformés de l'armée, exclus du service militaire en raison de la présence d'images anormales dans les radiogrammes du poumon avant induction.

L'objectif principal de l'étude était d'essayer de déterminer dans quelle mesure le radiogramme seul, sans l'aide des données de la clinique et du laboratoire, pouvait servir de guide pour estimer l'évolution ultérieure et par conséquent la signification clinique de lésions minimales découvertes dans les investigations concernant des collectivités ou des groupes.

Une classification des lésions tuberculeuses minimales fondée sur leur caractère pathologique fut utilisée, les éléments ont été groupés dans les trois catégories principales suivantes: (*a*) exudative et exudative-folliculaire; (*b*) folliculaire et fibro-folliculaire; (*c*) fibro-calcifiée et calcifiée.

L'évolution de ces lésions, c'est à dire leur progression, leur regression ou leur stabilisation, était déterminée en comparant le radiogramme initial avec le plus récent cliché effectué dans le but de faciliter cette étude.

Des variations caractéristiques dans l'aspect des lésions minimales paraissent en relation avec leur forme. Les taux de progression étaient les plus élevés dans la catégorie des formes exudatives et exudatives-folliculaires et les plus bas dans le groupe fibro-calcifié et calcifié. L'ordre inverse existait pour les taux s'appliquant à la stabilisation des lésions.

Outre la forme de la lésions, l'âge du malade paraissait avoir une signification. Les taux de progression les plus élevés furent observés parmi les sujets âgés de moins de vingt-cinq ans plutôt que chez ceux de vingt-cinq ans ou plus âgés.

Les limitations inhérentes à l'objectif de cette étude et au procédé employé ont été étudiées. En raison de la période de surveillance relativement courte des cas, et le fait que

l'analyse était uniquement limitée à une évaluation des signes radiographiques, cette étude ne paraît pas satisfaire aux nécessités essentielles d'une étude plus complète, et à longue échéance, de la valeur clinique et du pronostic de la tuberculose minimale.

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THE USE OF POTASSIUM IODIDE IN COMBINATION WITH STREPTOMYCIN IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS[1, 2]

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(Received for publication April 10, 1952)

INTRODUCTION

Recent interest has developed in the use of substances which might enhance the effectiveness of streptomycin in productive forms of tuberculous inflammation in which the tubercle bacilli are not readily available to the action of the drug. It was thought that potassium iodide might serve this purpose, for it has long been supposed that tuberculous lesions could be broken down by this salt. Several recent publications have appeared on the use of this combination of drugs (1–5). The results are somewhat contradictory, perhaps because of the variations in the materials and methods used for the studies.

The present writers have investigated the effects of potassium iodide in combination with streptomycin on experimental tuberculosis in guinea pigs under various conditions. Observations were made on the general course of the disease and on the gross and microscopic pathologic changes.

MATERIALS AND METHODS

The investigations consisted of five experiments following the same general protocol with certain pertinent variations among them.

All guinea pigs were young males obtained from commercial handlers or raised in this laboratory. The average weights of the groups varied according to the preliminary conditioning. All animals were kept in relative isolation, i.e., not directly exposed to tuberculous animals, for at least two weeks prior to experimental procedures.

In each of the experiments described below, the guinea pigs were divided into four or five groups of approximately 10 each in such a way that the average weights of the groups were very nearly the same. The groups were arranged as follows:

A. Untreated
B. Treated with 40 mg. of potassium iodide (KI) in capsule by mouth daily
C. Treated with 8 or 2 mg. of streptomycin (SM) intramuscularly daily
D. Treated with KI and streptomycin both as for *B* and *C*
E. Unvaccinated and untreated (when necessary).

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[2] This study was aided in part by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

All animals were tuberculin negative (to 0.1 mg. of Old Tuberculin intracutaneously) prior either to infection with 0.1 mg., moist weight, of *Mycobacterium tuberculosis* var. *hominis*, strain H37Rv, or to vaccination with BCG. The original culture of strain H37Rv was obtained from Dr. W. F. Drea of this laboratory and was subsequently carried on Long's synthetic medium. The infective dose of tubercle bacilli from a fourteen-day culture was diluted with physiologic saline so that it was contained in 1.0 ml. It was given subcutaneously in the flank, cephalad to the groin. If BCG had previously been given in the same manner, the virulent organisms were injected into the side opposite to the injection of the vaccine.

The potassium iodide was given by mouth in a capsule. The streptomycin was diluted so that the required daily dose was contained in 0.1 ml. A single daily injection was given intramuscularly in the rump alternately on the two sides.

All animals were weighed once a week, and notations were made of any lesions at the sites of injection of the bacilli and of any changes in general condition. Necropsies were done as soon as possible on all animals which died during the course of the experiment. All survivors were killed at the end of the experiments, and necropsies were done immediately on all animals. Observations were made of the gross pathology in most of the organs. Gross evaluation of the degree of tuberculous involvement of the lungs, liver, and spleen was made on the basis of plus to 4 plus. Brain examinations were made on some of the guinea pigs in *Experiment 2* and on most of those in *Experiments 3, 4, and 5*. Whole organs were fixed in 10 per cent formalin, and sections were made from the portion showing the most marked tuberculous involvement. Lungs, liver, and spleen of all animals which received streptomycin, with or without potassium iodide, as well as selected animals from the control groups, were studied microscopically. The over-all involvement of any given section, as determined microscopically, was evaluated on a basis of plus to 3 plus. Caseation necrosis, epithelioid cellular reaction, and fibrosis were similarly evaluated as indications of the animal's response.

When there was gross or microscopic evidence that the cause of death was a nontuberculous condition, such an animal was eliminated from the evaluation. Other cases in which there was microscopic evidence of nontuberculous disease were included because there was sufficient tuberculosis present to have caused death.

The animals were housed in cages containing 3 or 4 each. As they died, those within each group were consolidated with the idea of keeping those of approximately the same weight together. The food for each animal consisted of a 20 to 30 gm. portion of Purina Chow Checkers and a large handful of lettuce daily. Water was available *ad libitum*.

RESULTS

Preliminary Experiment (Experiment 1)

In a preliminary experiment, chemotherapy was begun three weeks after infection with H37Rv and was continued for five weeks. The daily oral dose of potassium iodide was 40 mg., and the daily dose of streptomycin was 8 mg. in one intramuscular injection. The surviving animals were killed three months after the end of treatment. The data for this experiment are summarized in table 1. In all experiments, the survival time was calculated from the day of infection with H37Rv.

General course of the disease: From the data presented in table 1, it may be seen that in *Group B* (KI) the tuberculosis progressed at approximately the same rate and to about the same degree as in the control animals of *Group A*. The animals in *Group C* (SM only) did well throughout the course of the experiment; they continued to gain weight during the entire time and there were no deaths. On the other hand, the animals in *Group D* (SM plus KI) did well during the course of treatment and for five weeks afterward. Up to this point, their clinical course

closely paralleled that of *Group C*. However, the condition of the animals in *Group D* (SM plus KI) then began to deteriorate, and 2 deaths from tuberculosis occurred before the experiment was terminated.

Gross pathologic findings: At necropsy, attention was centered on the lungs, liver, and spleen. In those animals in *Groups A* and *B* which died before the end of the experiment, there was at least two plus tuberculosis in the lungs, liver, and

TABLE 1

PRELIMINARY EXPERIMENT (EXPERIMENT 1)

GROUP	NUMBER OF GUINEA PIGS	TREATMENT (5 WEEKS)	SURVIVORS			AVERAGE SURVIVAL TIME*	AVERAGE INDEX OF GROSS PATHOLOGY				MICROSCOPIC EVALUATION
			End of Treatment	Three Months After Treatment			Lungs	Liver	Spleen	Total of Averages†	Total of Averages‡
						days					
A	10	—	8	2§	7 died‖	101	3.4	2.6	3.4	9.4	
					3 killed¶	145	3.0	1.7	1.8	6.5	
B	10	40 mg. KI daily	10	3	7 died	112	3.1	3.3	3.7	10.1	
					3 killed	145	3.7	2.5	3.3	9.5	
C	9	8 mg. SM daily	9	8§	0 died						
					9 killed	145	1.6	0.5	1.5	3.6	4.3
D	9	KI plus SM (as in *B* and *C*)	9	6§	2 died	123	3.0	2.3	3.0	8.3	4.3
					7 killed	146	1.7	0.9	1.3	3.9	

* Average survival time for those which died and for the survivors killed at the end of the experiment. Survival time calculated from the day of infection with H37Rv.

† Over-all involvement of each organ rated *plus to 4 plus*; *12* plus is the maximal index possible.

‡ Over-all involvement of each organ rated *plus to 3 plus*; *9* plus is the maximal index possible.

§ In *Groups A*, *C*, and *D*, one animal was killed three weeks earlier than the others in order to evaluate the progress of the disease. At the same time, one of *Group B* died and was available for the same purpose.

‖ Animals which died of tuberculosis during the course of the experiment either during or after treatment.

¶ Animals which survived until the termination of post-treatment observation period and which were then killed by ether.

spleen of all. In the few animals in *Groups A* and *B* which survived until the end of the experiment, there was less involvement of these three organs than in those which had previously died.

In the groups treated with streptomycin, with or without potassium iodide, there was definitely less extensive disease than in the control groups. In the 2 animals in *Group D* (SM plus KI) which died of tuberculosis, the pathologic changes were roughly of the same magnitude as in the control groups (*A* and *B*).

Although detailed notes were not made of lesions in other organs, tuberculous foci were not infrequently observed in the pericardium, mesentery, peritoneum,

kidneys, and testes. This was especially true in those animals in all groups which died of tuberculosis.

Microscopic pathologic findings: Sections of the lungs, liver, and spleen of all animals in *Groups C* and *D* (SM only and SM plus KI) and of one representative animal each in *Groups A* (control) and *B* (KI only) were examined histologically.

No significant differences could be demonstrated between the histologic pictures of *Groups C* and *D* (table 1). In each of these 2 groups, one guinea pig showed no evidence of tuberculosis in the lungs, liver, or spleen. In one animal in *Group C* and in two in *Group D*, there was evidence of tuberculosis in the lungs only; none in the liver or spleen. All others showed varying degrees of involvement up to a maximum (3 plus) of all three tissues.

Caseation necrosis occurred only in tissues in which the over-all involvement was extensive (2 plus or 3 plus). This change was considered as an indication of unfavorable response to the infection.

The presence of epithelioid cells was by far the most common finding, and occasionally it was coupled with fibrosis and caseation necrosis. This suggests that these animals, when assisted by an adequate dose of streptomycin, maintain an early stage of defense rather successfully. It was rather unexpected to find so little fibrosis in the tissues of those which received streptomycin alone. There was no difference in the amount of fibrosis present in *Groups C* and *D* (SM only and SM plus KI).

Central nervous system involvement: It was observed that one of the 2 guinea pigs in *Group D* which died of tuberculosis subsequent to treatment was paralyzed in the hind legs for four weeks just prior to death. At the time, the paralysis was considered to be due to a possible injury or perhaps to tuberculosis of the dorsal or lumbar vertebrae. However, at necropsy, no lesion of the spinal column or cord could be seen. In retrospect, because of observations in later experiments, it is now believed that this animal probably had a tuberculous meningitis. Unfortunately, the brain was not examined. No clinical involvement of the central nervous system was observed in any other animal in this experiment.

Summary of Experiment 1: Under the conditions of this preliminary experiment, it appears, therefore, that potassium iodide alone does not change the general course of progressive tuberculosis in the guinea pig; nor does it improve treatment when combined with streptomycin. In fact, in 2 instances, the combination of the two drugs was inferior to streptomycin alone. It is also apparent that five weeks is not a sufficiently long period of treatment, as demonstrated in animals which were observed for 3 months following treatment.

Influence of Immunization with BCG (Experiments 2 and 3)

The next two experiments were run simultaneously and were identical except in one respect. The animals in *Experiment 2* received BCG vaccine (5 mg. each subcutaneously) eight weeks prior to the infection with 0.1 mg. of H37Rv. The purpose here was to determine whether the behavior of the infection would differ if the animals were given some protection, as that obtained from BCG. Thus, conditions would simulate the more common immunologic situation in man. Treatment was begun five weeks after the virulent infection.

In contrast, the animals in *Experiment 3* received no preliminary vaccination and treatment was begun three weeks after virulent infection. The beginning of treatment was on the same day for both experiments, and from then on the two experiments were synchronized. Treatment (same dosages as in *Experiment 1*) was continued for seventeen weeks and

TABLE 2

INFLUENCE OF IMMUNIZATION WITH BCG (EXPERIMENT 2)

Groups A Through D Vaccinated with 5 Mg. of BCG Eight Weeks Prior to Infection with H37Rv

GROUP	NUMBER OF GUINEA PIGS	TREATMENT	SURVIVORS			AVERAGE SURVIVAL TIME*	AVERAGE INDEX OF GROSS PATHOLOGY				MICROSCOPIC EVALUATION
			End of Treatment	Six Months After Treatment			Lungs	Liver	Spleen	Total of Averages†	Total of Averages‡
						days					
A	9	—	7	2	7 died§	193	3.7	3.3	2.9	9.9	7.6 (6)¶
					2 killed‖	330	3.5	2.5	1.3	7.3	
B	9	40 mg. KI daily	5	1	8 died	173	3.0	3.2	3.4	9.6	7.6 (8)¶
					1 killed	330	4.0	4.0	2.0	8.0	
C	9	8 mg. SM daily	9	8	1 died	280	1.5	4.0	1.0	6.5	4.8 (9)¶
					8 killed	330	2.7	1.2	2.0	5.9	
D	9	KI plus SM (as in *B* and *C*)	9	9	0 died						
					9 killed	331	1.1	0.5	0.9	2.5	1.4 (9)¶
E	8	—	0	0	8 died	53**	3.6	2.2	2.1	7.9	

* Average survival time for those which died and for the survivors killed at the end of the experiment. Survival time calculated from the day of infection with H37Rv.

† Over-all involvement of each organ rated *plus to 4 plus*; *12* plus is the maximal index possible.

‡ Over-all involvement of each organ rated *plus to 3 plus*; *9* plus is the maximal index possible.

§ Animals which died of tuberculosis during the course of the experiment either during or after treatment.

‖ Animals which survived until the termination of post-treatment observation period and which were then killed by ether.

¶ Number in parentheses is the total number of individuals in the group examined microscopically.

** Pneumonitis, nonspecific, was a contributing factor in some of the early deaths in *Group E*.

the survivors were killed six months after the end of treatment. *Experiment 2* included a fifth group of animals which served as unvaccinated, untreated controls. The data for *Experiments 2 and 3* are summarized in tables 2 and 3.

General course of the disease: It may be seen in tables 2 and 3 that those animals treated with potassium iodide alone responded very similarly to the untreated animals irrespective of whether they had previously been vaccinated (*Groups A*

and *B* of both experiments). The average survival time for the vaccinated control groups was longer than for the unvaccinated. Not all of the vaccinated control animals died before the end of the experiment, but all of the unvaccinated control animals did. The members of the unvaccinated, untreated control group (*E*) in *Experiment 2* died surprisingly rapidly. The average survival time was only 53 days, the shortest was 26 days and the longest 138 days. Microscopic exam-

TABLE 3

INFLUENCE OF IMMUNIZATION WITH BCG (EXPERIMENT 3)

GROUP	NUMBER OF GUINEA PIGS	TREATMENT	SURVIVORS			AVERAGE SURVIVAL TIME*	AVERAGE INDEX OF GROSS PATHOLOGY				MICROSCOPIC EVALUATION
			End of Treatment	Six Months After Treatment			Lungs	Liver	Spleen	Total of Averages†	Total of Averages‡
						days					
A	9	—	2	0	9 died§	113	3.8	2.9	3.4	10.1	9.0 (5)‖
B	10	40 mg. KI daily	3	0	10 died	139	3.5	2.9	2.9	9.3	8.4 (10)‖
C	9	8 mg. SM daily	9	8	1 died	235	2.0	0.0	0.5	2.5	4.2 (9)‖
					8 killed¶	312	1.9	0.3	1.8	4.0	
D	9	KI plus SM (as in *B* and *C*)	8	4	5 died	200	2.2	1.3	1.8	5.3	5.6 (9)‖
					4 killed	313	2.2	1.1	1.9	5.2	

* Average survival time for those which died and for the survivors killed at the end of the experiment. Survival time calculated from the day of infection with H37Rv.

† Over-all involvement of each organ rated *plus to 4 plus*; *12* plus is the maximal index possible.

‡ Over-all involvement of each organ rated *plus to 3 plus*; *9* plus is the maximal index possible.

§ Animals which died of tuberculosis during the course of the experiment either during or after treatment.

‖ Number in parentheses is the total number of individuals in the group examined microscopically.

¶ Animals which survived until the termination of post-treatment observation period and which were then killed by ether.

inations of some of the animals which died early showed that a nonspecific pneumonitis was a contributing factor. Microscopic examination of the last survivor showed death to be due to typical tuberculosis.

The clinical courses of *Groups C* and *D* of the vaccinated series ran closely parallel except that one animal in *Group C* died of tuberculosis four months after the end of treatment and none of *Group D* died. In the unvaccinated series (*Experiment 3*) *Groups C* and *D* ran parallel courses until the end of treatment, after which they became divergent; 4 of 9 in *Group D* died, whereas only one in *Group C* died before the end of the experiment.

Gross pathologic findings: The post-mortem examinations of the organs of these

animals verified the observations on the general course of the disease. Among the animals of *Groups A* and *B*, in both the vaccinated and unvaccinated series, numerous tuberculous foci were found in the lungs, liver, and spleen (tables 2 and 3). There were no distinct differences among these four groups in the gross appearance of the lesions. The occurrence of caseation necrosis, confluency or discreteness of lesions, infarction, congestion, and hemorrhage was about equal.

Considering *Groups C* and *D* of *Experiments 2* and *3* from the standpoint of the gross pathology of the lungs, liver, and spleen, it may be seen in tables 2 and 3 that the organs from these animals showed less over-all involvement than in the control groups. The group which showed the least amount of tuberculosis in these organs was *Group D, Experiment 2*, in which the average index of gross pathology was 2.5. In contrast, the index of gross pathology for *Group C, Experiment 2*, was more than twice as high, namely, 5.9.

Groups C and *D* of *Experiment 3* did not show such marked contrast in respect to the gross pathology of the lungs, liver, and spleen. The animals in *Group C* showed somewhat less pathology, as one would anticipate from the number of survivors in the two groups.

More careful notations were made of lesions in the other tissues in these experiments than in the preliminary one. They were most often found in the testes. The next most common sites were the tracheobronchial and inguinal lymph nodes, the peritoneum, and the intra-abdominal nodes. Tuberculous lesions were also observed occasionally in the pericardium, kidneys and, rarely, in the adrenals.

Microscopic pathologic findings: Histologic sections were studied from the lungs, liver, and spleen of all guinea pigs in *Groups C* and *D* in both experiments and of selected animals in the control groups. The microscopic examinations of the brains are described on page 687.

Extensive tuberculosis was generally present in the tissues of the animals in the control groups. The most severely affected was *Group A, Experiment 3*, with *Group B, Experiment 3*, a close second. *Groups A* and *B, Experiment 2*, showed similar pathologic changes to a somewhat lesser degree.

The microscopic examinations of *Groups C* and *D* of *Experiments 2* and *3* showed definitely less pathology than was noted in the control animals. In the unvaccinated series, the *Group D* animals showed more pathology microscopically than the animals of *Group C*, as would be expected from the small number of survivors. As previously stated when considering other data for these groups, the treatment of the vaccinated animals of *Group D* (SM and KI) of *Experiment 2* was the most successful. This fact was substantiated by the microscopic examinations; 6 of the 9 animals in this group showed no tuberculosis of the lungs, liver, or spleen in the histologic sections. This statement must not be construed to imply that these 6 animals were completely cured of tuberculosis, because gross lesions of the testes were observed in 3 and all showed some degree of involvement of the lymph nodes. It is probable that the testes and lymph nodes, especially the tracheobronchial and the inguinal nodes, serve as reservoirs of tubercle bacilli from which progressive tuberculosis could subsequently develop.

The character of the necrosis was sometimes difficult to evaluate. In most

instances, it was of the caseous type and was surrounded by characteristic tuberculous granulation tissue. In a good number, however, the necrosis was of ischemic type and was often associated with fibrin and fibrinoid deposition. The margins showed congestion and, sometimes, thrombosed vessels but no cellular reaction of tuberculous character was present. The presence of the ischemic type of necrosis was more common in the controls of both series and seemed to be associated with a rapidly spreading and uncontrolled tuberculous infection. It was also found in a few of the unvaccinated animals treated with streptomycin and potassium iodide which died of tuberculosis, but it was rarely seen in those which survived until the end of the experiment even though definite tuberculosis was present. A third type of related lesion, less frequently seen, was that of abscess formation. With a few exceptions, the type of necrosis seen in *Groups C* and *D* of the two series was caseous.

Among the 8 groups considered here, necrosis of all types was more evident in the tissues of the animals of *Group A* of the vaccinated series and *Groups A*, *B*, and *D* of the unvaccinated series; and least in evidence in *Group D* (SM and KI) of the vaccinated series and *Group C* (SM only) of the unvaccinated series. The two groups with the least necrosis were the two most successfully treated.

Fibroblasts were most frequently seen in the control *Groups A* and *B* in the vaccinated series and in *Group A* of the unvaccinated series. They were least often seen in *Group D* (SM and KI) of the vaccinated series. The amount of fibrosis varied within wide limits among the different organs within the different groups. Thus, under the conditions of these experiments, potassium iodide alone appeared to have no inhibiting or lytic effect on fibroplasia.

There was no significant difference in the number of epithelioid cells between the two experiments or among the groups in each experiment.

Central nervous system involvement: Several of the unvaccinated animals developed paralysis of the hind legs or postural changes characterized by torsion or rotation of the head, or both, deviation of the eyes, listing of the entire body to one side, or forced movements to the right or left. Consequently, examinations of the brains were carried out on all animals which presented neurologic signs prior to death and on some of the others. Although no animals in the vaccinated series showed any signs of involvement of the central nervous system, certain brains were examined for comparative purposes.

The general procedure of these examinations was as follows: After the skin and muscles of the head had been reflected, a direct smear was made by searing through the nuchal ligament and spinal cord with a red-hot platinum needle. The top of the cranium was then removed and the cerebral hemispheres were gently reflected so that a smear and culture (on Corper's egg medium) could be made from the inferior surface of the brain. Notation was made of any gross lesion seen. The brain was then removed and put in 10 per cent formalin for sectioning.

The data for these examinations of the brains are summarized in table 6. If the number of animals which presented signs of neurologic disease before death is considered, it will be seen that these cases were more frequent among those

unvaccinated animals which received potassium iodide, regardless of whether or not they had received streptomycin. If the groups are considered separately, none which received streptomycin alone showed neurologic signs; 2 of the untreated controls were mildly affected; one of those which received streptomycin and potassium iodide was moderately affected; and 5 of those which received potassium iodide alone were severely affected. Stated differently, of those which received potassium iodide, 6 were moderately to severely affected; whereas, only 2 of those which did not receive potassium iodide were mildly affected.

In all cases in which there were definite clinical neurologic signs, the histologic sections showed tuberculosis of the meninges and of the subjacent parenchyma as well. Among these 8 cases, smears were positive for acid-fast bacilli in 5, negative in 3; cultures were positive for *M. tuberculosis* in 6, negative in one, and not done in one. Gross lesions of the parenchyma underlying the meningitis were found in the cerebellum, on the ventral surface of the cerebral hemispheres just anterior to the optic chiasm, and in the brain stem.

There was one case in *Group D* (SM and KI) in which no neurologic signs were observed prior to death but definite tuberculous meningitis and involvement of the subjacent parenchyma were seen both grossly and microscopically. The lesions involved the olfactory bulbs and extended into the right cerebral hemisphere. The culture was positive for *M. tuberculosis*.

In 2 other animals (*Group B*), the cultures from the brain surface were positive for *M. tuberculosis*, but there were no neurologic signs and there was no gross or histologic evidence of tuberculous meningitis seen in either case. The direct smears were also negative in these 2 cases. Since there was extensive tuberculosis in the other viscera and probable tuberculous bacteremia, these positive cultures could have resulted from puncture of the cranial vessels.

In 2 cases, infection of the inner ear was noted. Cultures of the ears were positive for tubercle bacilli in both cases. This suggests that the ear might be a focus from which the meningitis develops, although a hematogenous origin for the disease process in both locations cannot be excluded.

In striking contrast to the above findings for the unvaccinated series, the clinical behavior of all of the vaccinated animals and the pathologic and bacteriologic studies of the 7 brains examined were negative for tuberculous meningitis except for one smear listed as positive for acid-fast bacilli, probably due to technical error.

Summary of Experiments 2 and 3: If one compares the vaccinated series with the unvaccinated series, group by group, BCG vaccine is shown to produce a fair degree of protection even in the untreated animals. The use of streptomycin appeared to exert the greatest influence on the course of the disease. Potassium iodide considerably enhanced the effectiveness of streptomycin in the vaccinated series but was detrimental to the success of the streptomycin therapy in the unvaccinated series. Without streptomycin, potassium iodide was devoid of any therapeutic effect in either series.

Involvement of the central nervous system was confined to the unvaccinated series and was more frequent and more severe in those animals which received potassium iodide.

From these observations, it may be said that potassium iodide, when combined with streptomycin, appears to be of some use in the treatment of tuberculosis in BCG-vaccinated animals, but that it is deleterious when combined with streptomycin in the treatment of tuberculosis in unvaccinated guinea pigs.

Potassium Iodide and Subeffective Dose of Streptomycin (Experiment 4)

In all of the previous experiments, the daily dose of streptomycin was 8 mg., which is considered to be adequate for therapeutic purposes in the guinea pig. It was believed that

TABLE 4

POTASSIUM IODIDE AND SUBEFFECTIVE DOSE OF STREPTOMYCIN (EXPERIMENT 4)

GROUP	NUMBER OF GUINEA PIGS	TREATMENT	SURVIVORS			AVERAGE SURVIVAL TIME*	AVERAGE INDEX OF GROSS PATHOLOGY				MICROSCOPIC EVALUATION
			End of Treatment	Six Months After Treatment			Lungs	Liver	Spleen	Total of Averages†	Total of Averages‡
						days					
A	10	Saline and empty capsule	2	0	10 died§	99	3.8	1.8	2.2	7.8	8.4 (5)‖
C	10	2 mg. SM daily	6	0	10 died	161	2.7	1.2	1.3	5.2	6.8 (10)‖
D	9	40 mg. KI plus 2 mg. SM daily	5	0	9 died	154	2.5	1.9	2.1	6.5	5.8 (9)‖

* Average survival time for those which died and for the survivors killed at the end of the experiment. Survival time calculated from the day of infection with H37Rv.

† Over-all involvement of each organ rated *plus to 4 plus*; *12* plus is the maximal index possible.

‡ Over-all involvement of each organ rated *plus to 3 plus*; *9* plus is the maximal index possible.

§ Animals which died of tuberculosis during the course of the experiment either during or after treatment.

‖ Number in parentheses is the total number of individuals in the group examined microscopically.

the effects of combining potassium iodide with a subeffective dose of streptomycin should also be studied. For this purpose, daily doses of 2 mg. were used. In this experiment, using unvaccinated guinea pigs, only three groups were investigated: *A*, untreated controls; *C*, animals treated with a subeffective dose of streptomycin; and *D*, animals treated with the same dose of streptomycin plus 40 mg. of potassium iodide daily. No group treated with potassium iodide alone was included. In order to exclude any effect from the manipulations of administration of the drugs, the control group was given daily 0.1 ml. of physiologic saline intramuscularly and an empty capsule by mouth. Treatment was begun three weeks after the infection with 0.1 mg., moist weight, of strain H37Rv of the tubercle bacillus and was continued for seventeen weeks. The observations of these animals were continued for six months after the end of treatment. The data are summarized in table 4.

General course of the disease: All of the animals in all groups died before the end of the experiment. All of the untreated control animals were dead by the twenty-ninth week, with an average survival time of 99 days. Treatment with subeffective doses of streptomycin delayed death from tuberculosis in the animals of *Group C*; the average survival time was 161 days and the maximum was 252 days. The average survival time (154 days) for the animals of *Group D* was slightly less than for *Group C* even though one animal survived for 324 days. The saline and empty capsule treatment of *Group A* appeared to have no influence on the course of the disease.

Gross pathologic findings: The tuberculous changes found in the lungs, liver, and spleen upon gross inspection at necropsy were severe in *Group A* (controls) and somewhat less so in *Group D* (2 mg. of SM plus KI) and least in *Group C* (2 mg. of SM). The unusual distribution of more severe changes in the lungs than in the spleen and liver is noteworthy.

As before, lesions in other organs were of such frequency that attention should be called to them. The general pattern was the same as in the previous experiments. The tracheobronchial and inguinal lymph nodes and the testes were found to be most frequently affected; the peritoneum, intra-abdominal lymph nodes, and pericardium less often; and, rarely, the kidneys and adrenals. The bladder and penis were involved in one case.

Microscopic pathologic findings: Sections of the lungs, liver, and spleen in all animals in *Groups C* and *D* and in 5 in *Group A* were examined microscopically. Caseation necrosis was found mixed with the ischemic type of necrosis in the liver and spleen of some of the animals in all groups. In the lungs, the necrosis present was always caseous. The necrosis was most extensive in *Group A*. Evaluation of fibrosis and epithelioid cellular reaction provided no decisive, additional information.

Central nervous system involvement: In several instances in which tuberculosis of the thoracic and abdominal viscera was not very severe, tuberculous meningitis or meningo-encephalitis was the immediate cause of death. There were also instances in which the tuberculosis was severe in the other viscera as well as in the brain.

All brains, except 3 in *Group A* and one in *Group C*, were examined by the methods described for *Experiment 3*. These results are included in table 6. One animal in *Group A*, 5 in *Group C*, and 4 in *Group D* showed moderately severe clinical signs of neurologic disease. The most frequent type of involvement was paralysis of the hind legs one to six weeks prior to death. This occurred in 4 animals in *Group D* and 2 in *Group C*. The other 3 in *Group C* and the one in *Group A* manifested postural changes of a milder nature.

Gross lesions of the brain were found in all of the paralyzed animals except one (*Group C*) in which postural changes were observed for only one day prior to death (see below). Lesions were also found upon gross inspection at necropsy in some of the animals which showed no neurologic signs before death. There was one in *Group C* and 2 were in *Group D*. In all cases exhibiting neurologic signs before death or gross lesions of the brain, or both, tuberculosis of the meninges

and of the subjacent brain was seen in histologic section. There were 3 cases (one in *Group A* and 2 in *Group C*) in which the histologic examination showed tuberculous meningitis, 2 with subjacent encephalitis, but no gross lesions of the brain or any ante-mortem neurologic signs were observed.

In the one case mentioned above in which the signs were very transitory (one day only) and no lesion was observed at necropsy, the histologic examination and the smear and culture were all negative for evidence of tuberculosis. Possibly the postural change, which in this case was merely rotation of the head, was due to some temporary vestibular disturbance. It seems improbable that the dose of streptomycin used could have affected the vestibular nucleus of the eighth nerve.

In this experiment, the cultures more often confirmed the histologic evidence of tuberculosis than did the direct smears.

Summary of Experiment 4: This experiment verifies the fact that 2 mg. of streptomycin is therapeutically subeffective. It also confirms the findings in *Experiment 3* that potassium iodide in combination with streptomycin in unvaccinated guinea pigs is therapeutically ineffective or detrimental.

Subeffective Dose of Streptomycin in Vaccinated Animals (Experiment 5)

As *Experiment 4* repeated *Experiment 3* except for a decrease in the dosage of streptomycin, *Experiment 5* was designed to repeat *Experiment 2* except for a decrease in the dosage of streptomycin. In this experiment, BCG vaccine (5 mg. subcutaneously) was given to *Groups A, B, C,* and *D* six weeks prior to infection with 0.1 mg., moist weight, of H37Rv. Two days before the virulent infection, all vaccinated animals manifested mild to moderate (plus-minus to 2 plus) skin reactions to 0.1 mg. Old Tuberculin intracutaneously. The daily dose of streptomycin was 2 mg. intramuscularly; and of potassium iodide, 40 mg. by mouth. Both *Groups A* and *E* received 0.1 ml. of physiologic saline intramuscularly and an empty capsule by mouth each day. Treatment was begun five weeks after infection and continued for twelve weeks. The animals were observed for six months after the end of treatment. The data for this experiment are summarized in table 5.

General course of the disease: The virulence of the H37Rv was comparable to that in the previous experiments. The unvaccinated, untreated controls had an average survival time of 133 days and the vaccinated controls, untreated and treated with potassium iodide, had survival times and survival rates similar to those of the comparable groups in *Experiment 2*. The effect of the BCG vaccine on prolonging the survival time and decreasing the rate of mortality is again noteworthy.

The effect of a daily subeffective dose of streptomycin for a somewhat shorter period of administration was far less than that of the adequate dose as shown in *Experiment 2*. Approximately one-half of the animals treated with subeffective streptomycin, with or without potassium iodide, died before the end of the experiment. Potassium iodide seemed to have no effect on the survival rate.

Gross pathologic findings: For 2 groups the average indices of gross pathology were significantly less than for the controls. The average index for the 5 survivors in *Group C* was 5.8; and for the 4 survivors of *Group D*, 2.8. It is again demonstrated that the survivors which had been treated with both potassium iodide

and streptomycin after BCG vaccination had the least extensive involvement. This same relationship held true in *Experiment 2*; i.e., the survivors of *Group D* showed only approximately one-half as much disease as the survivors of *Group C*.

The gross lesions in viscera other than the lungs, liver, and spleen followed the same general pattern as in previous experiments. In every guinea pig, the lymph

TABLE 5

SUBEFFECTIVE DOSE OF STREPTOMYCIN IN VACCINATED ANIMALS (EXPERIMENT 5)

Groups A Through D Vaccinated with 5 Mg. of BCG Six Weeks Prior to Infection with H37Rv

GROUP	NUMBER OF GUINEA PIGS	TREATMENT	SURVIVORS			AVERAGE SURVIVAL TIME*	AVERAGE INDEX OF GROSS PATHOLOGY				MICROSCOPIC EVALUATION
			End of Treatment	Six Months After Treatment			Lungs	Liver	Spleen	Total of Averages†	Total of Averages‡
						days					
A	8	Saline and empty capsule	7	2	6 died§	198	3.2	2.4	2.1	7.7	8.0 (2)¶
					2 killed‖	312	3.0	2.0	3.0	8.0	
B	7	40 mg. KI daily	7	2	5 died	262	3.6	3.8	1.8	9.2	6.4 (3)¶
					2 killed	313	2.0	1.5	1.5	5.0	
C	8	2 mg. SM daily	8	5	3 died	249	4.0	2.0	3.0	9.0	8.4 (3)¶
					5 killed	314	1.9	1.6	2.3	5.8	4.5 (5)¶
D	8	KI plus SM (as in *B* and *C*)	8	4	4 died	237	3.7	2.8	3.5	10.0	7.5 (4)¶
					4 killed	315	1.0	0.4	1.4	2.8	3.0 (4)¶
E	9	As in *A*	6	0	9 died	133	3.7	2.2	2.1	8.0	7.3 (4)¶

* Average survival time for those which died and for the survivors killed at the end of the experiment. Survival time calculated from the day of infection with H37Rv.

† Over-all involvement of each organ rated *plus to 4 plus*; *12* plus is the maximal index possible.

‡ Over-all involvement of each organ rated *plus to 3 plus*; *9* plus is the maximal index possible.

§ Animals which died of tuberculosis during the course of the experiment either during or after treatment.

‖ Animals which survived until the termination of post-treatment observation period and which were then killed by ether.

¶ Number in parentheses is the total number of individuals in the group examined microscopically.

nodes were conspicuously involved, often with caseation necrosis which sometimes progressed to liquefaction. Outstanding examples were the tracheobronchial, the intra-abdominal, and the inguinal nodes. Other common sites of infection were the testes, peritoneum, omentum, and pericardium. The animals of *Group D* were almost free of lesions in these latter sites. There were no lesions in the testes; in the pericardium, lesions were present in only 2 cases; and in the peritoneum, in only one case. In *Group C*, 4 of 5 which survived until the end of the experiment had lesions in the testes and 3 of 5 had peritoneal lesions. In *Groups*

A and *B*, lesions of the testes were more frequently seen in the animals which died of tuberculosis than in the few survivors. In *Group A*, in 2 cases in which the gross pathology of the lungs, liver, and spleen was not extreme, the cause of death could well have been tuberculous infection of other viscera. In one case there was severe pericarditis and myocarditis; and in the other, severe peritonitis. Such cases explain the relatively low average index of gross pathology for the 6 animals of *Group A* which died of tuberculosis.

TABLE 6

INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN ALL EXPERIMENTS

GROUP AND EXPERIMENT	BCG-VACCINATED	NUMBER EXAMINED	NUMBER WITH NEUROLOGIC SIGNS BEFORE DEATH	NUMBER WITH GROSS BRAIN LESIONS	DIRECT SMEAR FOR ACID-FAST BACILLI			CULTURE FOR M. TUBERCULOSIS			MICROSCOPIC PATHOLOGY		TOTAL WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT
					Positive	Negative	Not Done	Positive	Negative	Not Done	Meningitis Only	Menings-encephalitis	
A, 2	+	3	0	0	0	2	1	0	2	1	0	0	0
B, 2	+	4	0	0	1?	3	0	0	3	1	0	0	0
A, 3	−	4	2	1	1	1	2	1	1	2	0	2	2
B, 3	−	10	5	2	5	4	1	6	2	2	1	4	5
D, 3	−	4	1	1	1	1	2	2	1	1	1	1	2
A, 4	−	6	1	1	2	4	0	1	2	3 (c)*	0	2	2
C, 4	−	9	5	4	4	5	0	3	2	4 (c)	2	5	7
D, 4	−	9	4	5	4	5	0	3	3	3 (c)	0	6	6
A, 5	+	8	0	0	0	6	2	0	6	2	0	0	0
B, 5	+	6	0	0	0	4	2	0	4	2	0	0	0
C, 5	+	7	0	0	0	2	5	0	2	5	0	0	0
D, 5	+	8	0	0	0	4	4	0	4	4	0	0	0
E, 5	−	9	0	1	1	8	0	1	8	0	0	1	1
Totals													
Vaccinated.....		36	0	0	1?	21	14	0	21	15	0	0	0
Unvaccinated.....		51	18	15	18	28	5	17	19	15	4	21	25

* (c) = Contaminated.

Microscopic pathologic findings: The microscopic evaluations of the pathology found in the lungs, liver, and spleen confirm the relative severities of the disease as seen grossly. Once again, the least amount of pathologic change was seen in the animals which survived until the end of the experiment in *Group D*, with the survivors of *Group C* showing only slightly more extensive disease.

Caseation necrosis was less often found in the animals treated with streptomycin than in the controls. All necrosis in the lungs and spleen was caseous; whereas, in the liver, abscess formation was sometimes associated with caseation necrosis

or sometimes the necrosis was of the ischemic type only. There was nothing remarkable about the frequency or intensity of the epithelioid cellular reaction except that there was less in the survivors of the 2 groups treated with streptomycin. Fibrosis was uniformly distributed among all groups except the unvaccinated, untreated control animals, in which little was present.

Two of the 5 survivors in *Group C* and 2 of the 4 survivors in *Group D* showed no microscopic evidence of tuberculosis in the lungs, liver, or spleen. In one survivor in *Group C*, the testes alone were severely involved.

Central nervous system involvement: There was no evidence, clinically or pathologically, of any involvement of the central nervous system in the vaccinated animals. Brains were examined grossly in all instances and bacteriologically in all animals which died of tuberculosis before the end of the experiment. No gross lesions were seen. There were no positive direct smears and only one culture was positive for *M. tuberculosis*. All of the brains which were examined histologically (21 cases) were negative.

On the other hand, among the 9 unvaccinated, untreated controls (*Group E*), although no guinea pig showed neurologic signs before death, the smear, culture, and gross and microscopic examinations were positive for tuberculosis in one case. Of the other 8 animals, the brains were bacteriologically negative; grossly, no lesions were seen; no tuberculous foci were seen in the 3 brains examined microscopically. These data are included in table 6.

Summary of Experiment 5: The combination of a subeffective dose of streptomycin with potassium iodide and increased host resistance due to BCG vaccination was therapeutically more effective than a subeffective dose of streptomycin plus increased host resistance but was not so effective as an adequate dose of streptomycin combined with the other two factors as in *Experiment 2*. There was only one case of tuberculous meningo-encephalitis observed, and that was in an unvaccinated, untreated control.

DISCUSSION

The results obtained under the given experimental conditions offer no substantiation for the theory of the mode of action of potassium iodide as presented by Jobling and Petersen (6, 7). Streptomycin rather than potassium iodide influenced the amount of necrosis. There were no differences in the other microscopic features, such as fibrosis and the epithelioid cellular reaction. Potassium iodide significantly improved the efficacy of streptomycin in vaccinated animals, but its mode of action was not apparent. Some light might be thrown on this question if animals were killed at selected intervals during the course of the experiment and at different stages of the evolution of the tuberculosis.

Perhaps the most significant finding in these experiments was that increased host resistance was necessary for potassium iodide to reinforce streptomycin. BCG vaccination appears to supply this defensive factor adequately. Several observations give proof to this statement.

(*1*) All vaccinated animals in *Experiment 5* showed some degree of cutaneous hypersensitivity when tested with Old Tuberculin prior to the infection with

H37Rv. (*2*) Caseous nodules appeared at the vaccination site; in some instances the nodules ulcerated. (*3*) The local reactions at the site of injection of H37Rv in the vaccinated animals were less severe than in the unvaccinated animals; i.e., ulceration occurred less often and healed more rapidly, and the caseous nodules disappeared more frequently. (*4*) The average survival time for the vaccinated controls was approximately twice as long as for the unvaccinated controls.

Variations in native resistance to tuberculosis in such a heterogeneous population of animals are to be expected. This was evidenced by a considerable variation in the length of individual survival time in the control groups. In order to obtain further evidence of the role of increased host resistance in the treatment with potassium iodide and streptomycin, the present experiments should be repeated on homogeneous strains of guinea pigs known to be resistant or susceptible to tuberculosis.

The tuberculosis in the guinea pigs treated with streptomycin was qualitatively similar to that found in the controls but was quantitatively less. Streptomycin was the major factor which ultimately brought about the control of the tuberculous infection. Its effectiveness was enhanced by the two other factors mentioned above, namely, potassium iodide and increased host resistance. In all experiments, if the animals which received streptomycin, with or without potassium iodide, are compared with those receiving no streptomycin, the gross and microscopic pathology is definitely less in the former. Furthermore, when an adequate dose of streptomycin was given, practically no ischemic necrosis[3] was seen. When necrosis was present, except in rare isolated instances, it was caseous. Ischemic necrosis was found, however, when a subeffective dose was used on unvaccinated animals; but, in these circumstances, the tuberculous process ultimately caused death in every instance.

At the end of treatment, the animals in those groups which received streptomycin alone and animals in those groups which received streptomycin plus potassium iodide appeared to be equally healthy. It seemed probable that, if the survivors had been sacrificed at this point, little difference in the effects of the two types of treatment would have been observed. Therefore, it seemed more suitable to observe these animals for a further period of six months in order to accentuate any differences in the course of the disease in the various groups. It is obvious that this type of procedure was successful, since the survivors at the end of the experiments on the vaccinated animals showed decided differences in pathology as described above.

In the microscopic studies, special attention was given to the evolution of "hard" tubercles as observed among other histologic changes by Feldman (8). He believed that such features as encapsulation, the presence of noncaseating or "hard" tubercles, fibrosis, and calcification indicated good control of the experimental infection. In some of the therapeutic studies cited by Feldman, a predominant type of tissue reaction of this character was observed. Analysis of the findings in animals in which the tuberculous process was considered to be non-

[3] See explanation on page 686.

progressive by all other standards, i.e., clinical course and gross studies at necropsy, failed to show a consistent reaction with a predominance of epithelioid cell tubercles as observed in the sarcoid lesion. In surviving animals with little or no gross pathologic changes, along with epithelioid cellular reaction and fibrosis, caseation necrosis was often present.

As far as the present writers have been able to ascertain, there has been little or no mention of tuberculous meningitis in the guinea pig resulting from virulent infection by the subcutaneous route. Steenken, Wolinsky, and Pratt (9) have produced this disease entity by the intracerebral route, as have others before them. The fact that meningitis was observed so frequently in the present experiments warrants thorough consideration. Although the frequency of occurrence of meningitis was only slightly greater in animals which received potassium iodide than in those which received no potassium iodide, the severity of the disease process was much greater. It seems probable that potassium iodide in some manner paved the way for the infection to invade the meninges and usually the subjacent parenchyma as well. Here again, a correlation was found between the effect of potassium iodide and the degree of host resistance, for, under the conditions of BCG vaccination, tuberculous infection of the meninges and subjacent brain was never observed. It would be valuable to study the occurrence of tuberculous meningitis in known resistant and susceptible strains of guinea pigs.

Intercurrent conditions, of which pneumonitis was the most common, resulted in the exclusion of 14 of the 210 animals from consideration in the present report. Included in the data are cases in which other pathologic conditions were seen concomitantly with the fatal tuberculosis. Polycystic liver of biliary origin occurred 3 times; nontuberculous infection of the lungs, twice. Severe fatty metamorphosis of the liver was not an uncommon finding and was considered to be secondary to the tuberculous process. Sprouting biliary channels were often seen in the liver and were interpreted as a reaction to uncontrolled tuberculous involvement.

There was no evidence that potassium iodide in any way influenced the virulence of the BCG vaccine. Thus far, no evidence of the emergence of streptomycin-resistant tubercle bacilli has been observed. In other experiments still in progress, this problem is being investigated more thoroughly and the findings will be reported in a later communication.

SUMMARY

The use of potassium iodide in combination with adequate or subeffective doses of streptomycin in the treatment of experimental tuberculosis in the guinea pig has been investigated. Unvaccinated and BCG-vaccinated animals were used. The animals were studied clinicall, and post-mortem gross and microscopic examinations were performed.

Under the conditions of the experiments, in unvaccinated animals potassium iodide appeared to be detrimental to the success of treatment with an adequate dose of streptomycin. In guinea pigs previously vaccinated with BCG, potassium iodide augmented the efficacy of streptomycin.

A subeffective dose of streptomycin, with or without potassium iodide, merely delayed death from tuberculosis.

Tuberculous meningitis and meningo-encephalitis were observed more frequently and were more severe in the unvaccinated animals which received potassium iodide than in the unvaccinated animals untreated or treated with a subeffective dose of streptomycin. Neurologic involvement was not observed in the unvaccinated animals which received an adequate dose of streptomycin or in any of the vaccinated animals.

No consistent differences in tissue reaction, gross or microscopic, could be demonstrated between the animals which received potassium iodide and those which did not receive potassium iodide.

The most successful treatment of experimental tuberculosis in guinea pigs in these studies depended on three factors: increased host resistance due to BCG vaccination; potassium iodide; and an adequate dose of streptomycin.

The question of variations in natural host resistance in heterogeneous populations of guinea pigs, particularly in relation to the use of chemotherapeutic agents, deserves further study.

SUMARIO

En Uso del Yoduro de Potasio en Combinación con la Estreptomicina en el Tratamiento de la Tuberculosis Experimental del Cobayo

Esta investigación versó sobre el uso del yoduro de potasio (KI), en combinación con dosis adecuadas o subeficaces de estreptomicina, en el tratamiento de la tuberculosis experimental en el cobayo. Usáronse animales vacunados con BCG y sin vacunar, estudiándoseles clínicamente y ejecutándose exámenes macro- y microscópicos después de la autopsia.

En las condiciones de este experimento, en los animales no vacunados, KI pareció ser adverso al éxito del tratamiento con una dosis adecuada de estreptomicina. En los cobayo previamente vacunados con BCG, el yoduro de potasio acrecentó la eficacia de la estreptomicina.

Una dosis subeficaz de estreptomicina, con o sin KI, meramente demoró la muerte debida a la tuberculosis.

Observáronse meningitis y meningoencefalitis tuberculosas más frecuentemente y en forma más grave en los animales sin vacunar que recibieron KI que en los dejados sin tratar o tratados con una dosis subeficaz de estreptomicina, mas no en los animales sin vacunar que recibieron una dosis adecuada de estreptomicina ni tampoco en los vacunados.

No pudo notarse ninguna diferencia constante en la reacción histológica, ya macro- o microscópica, entre los animales que recibieron y los que no recibieron KI.

En estos estudios, el éxito máximo del tratamiento de la tuberculosis experimental en los cobayos se basó en tres factores: mayor resistencia del huésped debida a la vacunación con BCG, yoduro de potasio, y dosis adecuada de estreptomicina.

Es acreedor a más estudios el punto de las variaciones de la resistencia natural del huésped en poblaciones heterogéneas de cobayos, en particular en relación con el empleo de agentes quimioterapéuticos.

RESUME

Utilisation de l'iodure de potassium en association avec la streptomycine dans le traitement de la tuberculose expérimentale chez le cobaye

L'emploi de l'iodure de potassium (KI) associé à la streptomycine à dose adéquate, ou d'un degré inférieur à la dose adéquate, a été étudié dans le traitement de la tuberculose expérimentale chez le cobaye. Des animaux non vaccinés et des animaux vaccinés par le BCG ont été utilisés. Ces animaux ont été étudiés cliniquement et il a été procédé, post-mortem, à des examens macro et microscopiques.

Dans ces conditions expérimentales, chez l'animal non vacciné, le KI est apparu comme défavorable au succès du traitement par la streptomycine à dose adéquate. Chez les animaux antérieurement vaccinés avec le BCG, l'iodure de potassium augmentait l'efficacité de la streptomycine.

Une dose de streptomycine inférieure à la dose adéquate, associée ou non au KI, ne servait qu'à retarder la mort par tuberculose.

La méningite tuberculeuse et la méningo-encéphalite furent observées plus fréquemment, et furent plus graves chez les animaux non vaccinés qui recevaient le KI que chez les animaux non vaccinés, non traités, ou recevant une dose de streptomycine inférieure à la dose adéquate; elles n'ont été observées ni chez les animaux non vaccinés qui recevaient une dose adéquate de streptomycine, ni chez aucun des animaux vaccinés.

Il n'a pas été démontré de différences spécifiques, macro ou microscopiques dans la réaction des tissus des animaux recevant l'iodure de potassium et de ceux qui n'en recevaient pas. Dans ces études, les résultats les plus favorables du traitement de la tuberculose expérimentale du cobaye dépendaient de trois facteurs: augmentation de la résistance du sujet due à la vaccination par le BCG; iodure de potassium; dose adéquate de streptomycine.

Le problème des variations dans la résistance naturelle du sujet dans les groupes hétérogènes de cobaye, particulièrement en ce qui concerne l'emploi des agents chimiothérapeutiques, mérite de plus amples études.

Acknowledgments

It is a pleasure to acknowledge the generosity of Dr. J. D. Aronson of The Henry Phipps Institute of Philadelphia who supplied the BCG vaccine.

The potassium iodide capsules and the streptomycin sulfate were furnished through the cooperation of Dr. J. M. McGuire by Eli Lilly and Company.

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THE EFFECT OF IODIZED OIL BRONCHOGRAPHY ON THE SUBSEQUENT COURSE OF PULMONARY TUBERCULOSIS[1, 2]

A Review with a Study of 49 Cases

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(Received for publication April 10, 1952)

INTRODUCTION

It is generally agreed that collapse therapy of pulmonary tuberculosis, with the employment of such procedures as pneumothorax, pneumonolysis, pneumoperitoneum, and thoracoplasty, will not uniformly bring about cavity closure and disappearance of tubercle bacilli from the sputum. In selected cases of early disease, satisfactory results are obtained in a fairly high percentage of patients submitted to collapse therapy; while in those with pulmonary tuberculosis of long standing, failures are more frequent. Such failures apparently are not due to the extent of the tuberculous lesion or the size or position of the tuberculous excavation, but are rather the result of irreversible changes which have occurred in the structures of the bronchi of the involved segment, lobe, or lung. There is sufficient evidence that such bronchial changes occur, with high frequency, in patients with pulmonary tuberculosis as may be demonstrated by bronchoscopy, bronchography, or the careful study of both surgical and necropsy material.

It becomes apparent, therefore, that patients considered for collapse therapy, particularly for such an irreversible procedure as thoracoplasty, should undergo extensive preoperative investigation, not only of the lung parenchyma, by physical and roentgenographic examination to determine the extent of the disease and the presence of excavation, but particular effort should be directed toward demonstrating any associated bronchial lesions such as ulceration, stenosis, or fixed dilatation of the segmental, lobar, or main bronchi. These lesions cannot be visualized by ordinary roentgenographic study, while bronchoscopy allows examination of only a small area of the proximal portion of the tracheobronchial tree. Bronchography is well adapted for a more complete exploration of the entire tracheobronchial tree and will consequently demonstrate lesions beyond the point of visualization by bronchoscopy. The more uniform application of bronchography in patients with pulmonary tuberculosis undergoing collapse therapy will greatly reduce the high incidence of failure of this procedure. Patients in whom bronchography has demonstrated extensive bronchial disease may then be subjected to primary resection without first applying the time-consuming trial of collapse therapy, obviously leading to eventual failure.

Although the value of contrast visualization of the tracheobronchial tree in both tuberculous and nontuberculous diseases of the lung is generally admitted,

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[2] Aided by a grant from The Comly Fund for Research of The Ohio State University.

there is considerable reluctance among clinicians to apply bronchography, utilizing an iodized oil, in patients with pulmonary tuberculosis. The chief reason for such apprehension is apparently based on the generally held opinion that iodine administration to patients with pulmonary tuberculosis has an unfavorable effect upon the course of this disease. It has also been stated that the introduction of iodized oil into the tracheobronchial tree may result in bronchogenic spread of the infection or lead to reactivation of an apparently healed focus of tuberculosis. Moreover, the persistence of contrast media in the alveoli and bronchioles of the lung following bronchography greatly interferes with subsequent roentgenographic study of tuberculous lesions. Occasional unfavorable effects of bronchography, such as cocaine reactions, anaphylactic shock, and acute iodism, have been reported.

A critical review of the literature was consequently undertaken to determine any basis for the generally held opinion that iodized oil bronchography has an unfavorable effect on the subsequent course of pulmonary tuberculosis. A clinical study of a series of 49 patients with active pulmonary tuberculosis was also conducted in order to investigate the effect of the high blood iodine concentration consequent to lipiodol bronchography on the course of the associated tuberculous lesions.

REVIEW OF THE LITERATURE

Lipiodol (Lafay) was first employed as a diagnostic agent in 1922 by Sicard and Forestier (1). Armand-Delille and Moncrieff (2) subsequently reported one case of iodism and Landau (3) reported two cases of mild iodism. Lauret, Secousse, and Caussimon (4) noted an improvement in the general health and a decrease in the temperature and expectoration following lipiodol bronchography in patients with profusely suppurating cavities. They stated that patients with rapidly progressive pulmonary tuberculosis or with cachexia sometimes developed dyspnea, polypnea, cyanosis, increase in fever, collapse, and death in four to twenty days following the intratracheal instillation of iodized oil. Archibald and Brown (5) reported a case of fatal tuberculous pneumonia following the bronchoscopic administration of lipiodol into the tracheobronchial tree of a patient with pulmonary tuberculosis. Miller and Eglee (6) encountered two cases of acute iodism in several hundred bronchographies. They observed no deleterious effects from the use of lipiodol, even when the oil was retained for several months. Geer, Callahan, and Gardiner (7) concluded that lipiodol could be used with safety in patients with tuberculous fistulas, tuberculous empyematous cavities, and chronic pulmonary tuberculous lesions.

Amberson and Riggins (8) pointed out that lipiodol may be retained in the alveoli for years and that a clinically harmless, slight exudative reaction usually occurs in the areas of retained lipiodol. They stated further that intratracheal instillation of lipiodol can disseminate or aggravate the lesions of pulmonary tuberculosis. Singer and Francis (9) encountered no reactions following the use of lipiodol in thirty-five patients with chronic pulmonary tuberculosis. Neuhoff (10) advocated preoperative study by lipiodol bronchography of patients with pulmonary tuberculosis. Murphy (11) used lipiodol in the examination of ninety-nine patients with pulmonary tuberculosis, and encountered no major complication. He recommended the use of lipiodol in pulmonary tuberculosis except in cases of acute pulmonary tuberculosis with fever, in patients with debility, and in patients with recent hemoptysis.

Cabitt, Singer, and Graham (12) observed no serious effects after using lipiodol over a period of several years in patients with pulmonary tuberculosis, and they highly recommended bronchography before and after thoracoplasty. Bernard (13) stated that the continued persistence of lipiodol in the lung is no cause for concern, but Schneider and Segal (14) reported that pulmonary tuberculosis developed around an area of retained lipiodol in a patient who was roentgenographically free of pulmonary tuberculosis at the time lipiodol bronchography was done, eighteen and twelve months earlier. Boyer (15) performed fifty-two separate instillations in forty-six patients with pulmonary tuberculosis and observed no spread of the tuberculous process which could be definitely attributed to iodized oil bronchography. Dormer, Friedlander, and Wiles (16), after instilling radiopaque substances into the bronchi of patients with pulmonary tuberculosis over a period of twenty-five years, concluded that the method was safe and that no case was made worse by the use of lipiodol.

The Local Reaction Caused by Lipiodol

The iodine of lipiodol is chemically bound in the poppyseed oil and presents none of the chemical or physical properties of elemental iodine. It is nontoxic and nonirritating when not in a deteriorated state.

Santé (17) found that bronchial tissue tolerated lipiodol well. Graham, Singer, and Ballon (18) quote the work of H. C. Ballon on the effects of lipiodol on the bronchial and parenchymal tissue of the lungs of rabbits. No ill effects were noted and no inflammatory reaction could be demonstrated macroscopically or microscopically in the lungs of normal rabbits following intratracheal instillation. Retained lipiodol was found to remain unchanged for weeks or even months. Fried and Whitaker (19) and Brown (20) found that lipiodol remained in the lungs of cats for long periods of time, producing a phagocytic response without sclerotic changes. Pinkerton (21) demonstrated that iodized vegetable oils produced no evidence of reaction in the lungs of puppies and rabbits. Bezancon, Delarue, and Vallet-Bellot (22) examined the lungs from three patients dying two days, twelve days, and six years, respectively, after the instillation of iodized poppyseed oil. They were able to demonstrate residual oil but no striking tissue response other than the presence of lipophages. Patterson (23), conducting an extensive study on the response of lung tissue to oily substances, concluded that poppyseed oil containing 40 per cent iodine called forth but little reaction. Phagocytosis was found to be slight.

That lipiodol is locally innocuous to the bronchopulmonary tissue of patients with pulmonary tuberculosis is attested by many (6, 7, 9, 10, 11, 12, 13, 15, 16). Nevertheless, reports of local reactions are still to be found in the literature. Amberson and Riggins (8) noted slight exudative reactions around areas of retained lipiodol, but concluded that these were of no consequence. Schneider and Segal (14) reported that pulmonary tuberculosis had developed in the neighborhood of retained lipiodol in a patient who had received lipiodol eighteen and twelve months earlier and who had been found to be roentgenographically free of tuberculosis at the earlier periods. They assumed a causal relationship between the retained lipiodol and the development of pulmonary tuberculosis and postulated that the prolonged presence of lipiodol probably reactivated a nonclinical tuberculous process and converted it to manifest disease. They quoted the work of Sweany (24), who showed that many small encapsulated foci containing tubercle bacilli will not be detectable roentgenographically, although they may be detected on post-mortem examination. Schneider and Segal assumed that their patient had such a lesion.

Rabinovitch and Lederer (25) gave lipiodol to an old patient who died later of bron-

chopneumonia. At autopsy the lungs showed changes resembling a lipoid pneumonia. Wright (26) found necropsy evidence of reticular tissue reaction, parenchymal tissue fibrosis, and pleural hyalinization, around areas of lipiodol. The oil had been entrapped for twelve months in bronchiectatic cavities of the right lower lobe in a patient with an epithelioma of a lateral branch of the right bronchus. Lipophages were also present, but no bronchial epithelial reaction was noted. Commenting on this unusual reaction to lipiodol, Frieman, Engleberg, and Merrit (27) suggested that the picture was one of the normal walling-off of a foreign body which could not be removed, rather than a reaction which could be attributed to the chemical nature of the oil.

Brody (28) reported multiple foci of lipid granulomatous reaction in the middle and lower lobes of a right lung, resected for carcinoma of the bronchus, one month after the diagnostic instillation of iodized poppyseed oil. The bronchi of these lobes were partially obstructed by the tumor. Two other pneumonectomized lungs were examined, but no similar lesions were found. Beatty and Baily (29) found an area of firm rubbery tissue surrounding the dilated bronchi of the posterior segment of the right lower lobe, resected three days after a lipiodol bronchogram. Microscopic section revealed an extensive granulomatous reaction within which were pseudo-tubercles containing amorphous acidophilic caseous centers and numerous foreign-body giant cells. A similar granulomatous process was observed by Storrs, McDonald, and Good (30) in a patient three weeks following bronchography with iodized and chlorinated peanut oil.

Acute Iodism and the Spread of Pulmonary Tuberculosis

Miller and Eglee (6) and Amberson and Riggins (8) state that acute iodism results largely from the *absorption by the gastrointestinal tract* of the iodine from the lipiodol that is swallowed after coughing, rather than from the absorption by the bronchial mucous membrane of the lipiodol that remains in the bronchopulmonary tree. Santé (17) maintains that the simple epithelial lining of the alveoli is not very effective in absorbing lipiodol and that removal of retained lipiodol is largely by phagocytosis and lymph drainage. Lipiodol in the lungs is gradually discharged through the bronchi (8). Archibald and Brown (5), in experiments with cats, found that lipiodol can be absorbed from the bronchial and alveolar lumina, but they did not state the extent to which this occurs.

Balyeat and Seyler (31) did not observe any increase in the urinary excretion of iodine after the administration of lipiodol to two anesthetized dogs through a dissected and isolated trachea, and they concluded that the iodine of the iodized oil does not pass through the bronchial mucous membrane. Cole, Dunn, and Curtis (32) were unable to note any significant rise in the blood iodine of dogs given lipiodol after the esophagus and upper end of the trachea had been cut across and ligated. They concluded that iodine combined with a lipoid substance is absorbed but little from the broncho-alveolar tree, if absorbed at all. Marchese, Klassen, and Curtis (33) were able to demonstrate a definite lowering of the increased blood iodine subsequent to bronchography by the use of cathartics, postural drainage, and gastric lavage during the immediate post-lipiodol period.

The occurrence of acute iodism following lipiodol bronchography is not frequent, but it does occur and cases are still being reported. Nine fatal (8, 34, 35, 36, 37, 38, 39) and sixteen nonfatal iodine reactions (14, 36, 40, 41, 42, 43, 44) occurring in nontuberculous patients following the intratracheal instillation of lipiodol have been reported. That the cause of death was due to an allergic reaction to iodine is questioned in six of the nine fatal cases. No reports of a fatal outcome and but five nonfatal iodine reactions (2, 3, 6) following the use of lipiodol (8, 35, 37, 38, 39) in patients with pulmonary tuberculosis have been reported. The incidence of nonfatal iodine reactions is undoubtedly higher, yet no addi-

tional reports of its occurrence could be found. The reactions encountered by Boyer (15) following the administration of lipiodol to five patients with pulmonary tuberculosis and emphysema were not included by the present writers. It is believed that the reactions described were due either to Pontocaine, to the temporary mechanical blocking of available respiratory epithelium in emphysematous patients, or to the pharmacologic action on the respiratory epithelium of the iodine that was absorbed. In all of the reported reactions to iodine, no data were found to indicate that the reaction had caused spread of the tuberculous process. Acute iodism following the use of lipiodol in a patient with active minimal pulmonary tuberculosis did not produce extension of the original pulmonary infiltration (44).

Bastedo (45) found that tuberculous necrotic tissue takes up more iodine than do other tissues; however, Wells and Long (46) were unable to confirm such chemical specific binding of iodine in tuberculous tissue. Jobling and Petersen (47) expressed the opinion that, both in the blood and in necrotic tissue, iodine combines with and renders inert the anti-trypsin which is the normal preventive of the resolution of necrotic tissue. As a result, the caseous matter is subjected to the action of the tryptic ferments and is digested and absorbed. Clinically, Goldberg (48) advocated the use of iodine in tuberculosis for many years without noting any deleterious effects from its use. Featherston (49) observed the effects of potassium iodide on experimentally induced omental tubercles and found no evidence that the iodides caused any breakdown or resorption.

The Role of Lipiodol in the Mechanical Spread of Pulmonary Tuberculosis

Lipiodol is neither bactericidal nor bacteriostatic. Neuswanger (50), as well as Archibald and Brown (5), found that organisms grew in, and in close proximity to, globules of the oil.

Coughing during and following lipiodol bronchography causes widespread dissemination of the oil (6). Reinberg (51) noted the spread of lipiodol from one lobe to another, from one side to the other, and from the base to the apex. Ameuille (52) actually observed this spread through the fluoroscope. Ballon, Guy, and Elder (53) made roentgenographic observations of the projection of the oil from the lower lobes throughout the entire lung, even to the apices.

Following coughing, the bronchogenic spread of tubercle bacilli along with the lipiodol is stated by some as a possible danger to the use of iodized oil in patients with pulmonary tuberculosis. Lichtwitz (54) reported an acute extension following the use of lipiodol in a patient with pulmonary tuberculosis, and consequently warned against the unwarranted use of lipiodol. Armand-Delille and Gelston (55) also warned against the use of lipiodol in active pulmonary tuberculosis. Archibald and Brown (5) reported the occurrence of tuberculous pneumonia following the bronchoscopic injection of lipiodol. Amberson and Riggins (8) stated that in tuberculosis, as well as in acute and chronic suppuration, dissemination and aggravation might be caused by lipiodol.

Others see no danger in the use of lipiodol for bronchography. Miller and Eglee (6) used lipiodol in several hundred tuberculous patients and did not encounter bronchogenic spread. Geer, Callahan, and Gardiner (7) used lipiodol in twenty patients with chronic pulmonary tuberculosis and concluded that the use of lipiodol was safe in patients with chronic lesions. Singer and Francis (9) examined thirty-five patients with chronic pulmonary tuberculosis with lipiodol, and in none of these were there noted any serious after-effects.

Murphy (11) encountered no major complication following the administration of lipiodol to ninety-nine patients with pulmonary tuberculosis. Neuhoff (10) found the use

of lipiodol to be safe, and stated that pulmonary tuberculosis is not completely studied preoperatively if a bronchographic examination is not made. Cabitt, Singer, and Graham (12) used lipiodol for several years in patients with pulmonary tuberculosis without encountering any serious after-effects. Boyer (15) examined forty-six tuberculous patients with lipiodol and observed no spread of pulmonary disease which could definitely be attributed to the procedure. Dormer, Friedlander, and Wiles (16) instilled radiopaque substances into the bronchi of approximately 2,000 patients over a period of twenty-five years, and concluded that none were made worse by the procedure.

Since it has been shown that lipiodol can readily be disseminated by coughing, it seems logical to assume that the sputum of patients with active pulmonary tuberculosis can also be disseminated to other parts of the lung. Ching and T'ang (56), in their analysis of 242 patients with unilateral pulmonary tuberculosis which subsequently became bilateral, pointed out that infection may pass from the right lung to the left, as well as in the opposite direction, but that sputum and cough must be present. They also pointed out that cough more or less completely and immediately evacuates loose detritus, mucus, and excessive secretions from cavities during the waking hours. When the cough reflex is inhibited, as in sleep or sedation, immediate evacuation of material entering the bronchi does not occur. The material gravitates to the lowermost portion of the lung and is distributed after the re-establishment of the cough reflex to points of predilection on the right and left, depending on which side is diseased and on which side the patient is lying. The points of predilection for bronchogenic spread are the second anterior interspace on the right and the third anterior interspace on the left.

If the dissemination of tubercle bacilli were the only factor responsible for bronchogenic spread of disease, then more frequent and more numerous spreads should be observed roentgenographically in patients with sputum rich in tubercle bacilli. The present writers have observed patients with far advanced pulmonary tuberculosis, with many bacilli in the sputum, who developed bronchogenic spread early and eventually died of their pulmonary tuberculosis in spite of attempted treatment. Others developed early spread of disease, but, aided by bed rest and collapse therapy, were able to arrest or heal their lesions. Still others did not develop bronchogenic spread, even though the sputum was rich in tubercle bacilli and a cavity was present. Collapse therapy aided these patients in arresting their lesions. In all cases, the presence of an abundance of tubercle bacilli in the sputum increased the opportunity for bronchogenic spread; nevertheless, spread of disease occurred only in certain patients. It became evident that other factors, in addition to the dissemination of tubercle bacilli into uninvolved portions of the lung, were important in determining whether or not a new tuberculous lesion would develop. A list of these factors consequently follows:

Resistance of the patient: The level of resistance which a patient is able to develop, as well as the relationship of that resistance to the underlying infection, will determine to a great extent whether new lesions will develop. A low level of resistance, or a resistance which is inadequate concerning the particular infection, will permit seeding with tubercle bacilli. The level of resistance which a patient acquires may decrease under certain conditions. Rich (57) points out that the power of the body to inhibit proliferation of bacilli and spread of disease may be diminished at any time under adverse conditions (malnutri-

tion, physical overstrain, mental overstrain, the presence of intercurrent infection, and chronic alcoholism). The degree of susceptibility varies greatly from time to time and corresponds to the variations in the degree of resistance. Spread may consequently occur during periods of increased susceptibility.

Size of the inoculum of tubercle bacilli: The size of the reinfecting dose exerts a marked influence on the initiation and outcome of tuberculous lesions (57). Large numbers of tubercle bacilli which remain in any area for a period of time will overcome whatever resistance the patient has and cause the development of new lesions. Bronchogenic spread is not likely when the sputum is persistently negative for *M. tuberculosis*. It may or may not occur when tubercle bacilli are present in the sputum, the concentration of tubercle bacilli and the level of acquired resistance being among the determining factors.

Degree of hypersensitivity: The reaction to a certain number of bacilli is more pronounced in the person hypersensitive to tuberculin than in the less sensitive person (57). Tuberculin hypersensitivity in itself is not of primary importance in the consideration of bronchogenic spread of disease. It comes into play once tubercle bacilli are able to initiate a new focus, at which time it will determine, to a degree, the extent of the reaction that will take place. Whether or not new foci will develop will depend on the patient's resistance and on the dosage of tubercle bacilli to any particular area.

Virulence of the tubercle bacilli: Virulent tubercle bacilli are able to multiply rapidly and, by their rapid multiplication, increase the dose of tubercle bacilli to a particular area. There will be a tendency for local resistance to be overpowered and, once a new focus has been established, for local growth and extension of the tuberculous process to take place.

Degree of cough: The general tendency of the body is to expel lipiodol, along with secretions from the tracheobronchial tree, chiefly through the mechanism of cough. Most of the lipiodol is eliminated by coughing (8). Lipiodol persists in the lungs on the average of ten to fourteen days (7), but its persistence in the parenchyma has been observed for as long as three years (15).

Jackson (58), from bronchoscopic examinations, found that the finer subdivisions of the tracheobronchial tree produced less cough when stimulated by instrumental contact than did the larger bronchi. Reinberg (51) and Brown and Archibald (59) found that cough is produced only when the larynx, trachea, and the bronchi of the first and second order are stimulated.

Material is moved from the less sensitive areas to the larger bronchi by many mechanisms. During cough, the sudden opening of the glottis, after the intra-aveolar pressure has been increased during the pre-expiratory phase, causes a sudden expulsion of air from the alveoli. The secretions or materials present in the alveoli and bronchioles thus tend to be pushed into the larger bronchioles and into the bronchi, and serve as stimuli for further coughing. The elastic recoil causes a narrowing and shortening of the bronchi during expiration, thereby lessening the available space for intrabronchiolar secretions and permitting spillage of the secretions into more sensitive areas. The contraction of the bronchial musculature at the end of expiration squeezes secretions out toward the larger bronchi. If the materials in the alveoli are irritating, bronchorrhea will result, and the spilling over of the secretions into more sensitive areas will initiate cough and cause the expulsion of the irritants. Ciliary action also aids in the expulsion of materials and secretions from the large bronchioles and from the bronchi. Those materials which cannot be removed by the above mechanisms will be eventually removed by phagocytosis, or will be rendered harmless by tissue reaction.

Lemon (60) states that lipiodol is removed from the lung mainly by coughing, ciliary

action, and actual peristaltic movements of the tracheobronchial tree. Applebaum (61) showed that, if the cough reflex is depressed either naturally or because of alcohol or sedation, the chances for the development of a lung abscess are great. It follows that the depression of the cough reflex for sufficient periods of time in patients with pulmonary tuberculosis and sputum rich in tubercle bacilli will result in the intrapulmonic accumulations of infective secretions and in the subsequent spread of the tuberculous process. Such a depression of the cough reflex, or of ciliary action and bronchial peristaltic movements, occurs in cachetic patients, in patients under heavy sedation, and in patients who have undergone prolonged operative procedures under general anesthetics. The use of lipiodol in cachetic or heavily sedated patients may possibly lead to bronchogenic spread of tuberculous lesions. Patients displaying a vigorous cough will be less likely to develop post-lipiodol spread of disease, if their resistance is adequate.

Brown and Archibald (59) showed that cough may acutely spread semiviscid material deeper into the pulmonary tree, rather than expel it, during both the expiratory effort and the inspiratory intake of air. They also showed that thick, tenacious sputum resists this action, and that it remains in the larger bronchi from which it is expelled. In patients with pulmonary tuberculosis, the thick tenacious sputum is expelled from the bronchi and is not driven deeper by cough. Whatever bronchogenic spread of disease then occurs must have as its incitant tubercle bacilli which lie free in the bronchi and which are mixed and disseminated along with the lipiodol during coughing, or tubercle bacilli contained in globules of mucus of a size sufficiently small to be driven deeper into univolved portions of the lungs during coughing. Whether or not true seeding will occur will depend on the number of tubercle bacilli present in the retained mucus or lipiodol or the virulence of the tubercle bacilli and on the resistance of the patient. The continued presence of a vigorous cough will tend to prevent the stasis of infective material for the period of time necessary for seeding to occur, or, by piecemeal evacuation of the infective materials, will so reduce the number of the tubercle bacilli which can cause new infection in any particular area that resistance will prevent seeding.

Character of the sputum: Goldberg (62) states that expectoration is not always present in tuberculosis and that its absence or presence depends on the character of the tuberculous process. Sputum is plentiful in the caseous-pneumonic, and scant in both the exudative and productive forms.

In exudative tuberculosis, in which there is comparatively little lung necrosis, tubercle bacilli are found in the sputum only in the first days of the infection. In the exudative productive type of tuberculosis, tubercle bacilli may be demonstrated early; but later, if expectoration ceases, they cannot be found in the sputum (63). In the chronic productive type of tuberculosis, the infection is in the terminal bronchioles (64). When these small nodules ulcerate, only a few tubercle bacilli are discharged. In the early stages the sputum is scant and tubercle bacilli are difficult to demonstrate. In the late stages, when emphysema and chronic bronchitis may be present, there is copious expectoration but no tubercle bacilli are found in the sputum. In the acute stage of caseous pneumonic tuberculosis (65), expectoration is profuse and laden with tubercle bacilli. In the chronic stage, after evacuation has occurred, expectoration is more or less profuse and tubercle bacilli are easily demonstrated.

Character of the underlying lesions: The presence and concentration of tubercle bacilli in the sputum will be determined by the character of the underlying lesions. Caseous pneumonic lesions usually produce a profuse sputum with an abundance of bacilli, but atelectasis of the involved lobe or lobes because of the tracheobronchial disease, or cavity closure by collapse therapy, will diminish the quantity of sputum and the concentration

of tubercle bacilli. The lower the bacillary content of the sputum, the less tendency is there for bronchogenic spread of disease following the use of lipiodol, provided that the patient's resistance is adequate. Stenosis of a bronchus supplying a diseased segment or lobe will prevent extrasegmental or extralobar bronchogenic spread of disease, provided that the tubercle bacilli have their source in those regions and that the stenosis is complete. Nevertheless, spread of disease within the blocked segment or lobe will occur, and its extent will be determined by the location of the stenosis. Tracheobronchial disease may serve as a focus for the further spread of the tuberculous process, especially when ulceration is present. The use of lipiodol at a time when the bacillary content of the sputum is high because of the tuberculous bronchial ulceration may or may not result in bronchogenic spread of the disease, depending on those factors already discussed. Partial bronchial stenosis may cause the entrapping of both lipiodol and infective material distal to the narrowed opening, and will most likely result in a spread of tuberculosis in the area distal to the partial block.

Effectiveness of collapse therapy: An adequate collapse procedure will lessen the concentration or even cause the disappearance of tubercle bacilli from the sputum. If bacilli persist in the sputum, spread of disease may or may not occur, depending on the relationship between resistance and infection in a patient aided, but not rendered noninfectious, by collapse therapy.

CLINICAL STUDY

The following study was conducted to determine the effect, if any, of the increased blood iodine concentration consequent to intratracheally instilled lipiodol on the course of pulmonary tuberculosis. An unselected group of 49 patients with active pulmonary tuberculosis undergoing diagnostic lipiodol bronchography was the basis for study. The bronchographies were performed during the period from December, 1945, to January, 1947, and all patients were carefully observed until May 1, 1947, unless separation from the hospital occurred earlier. Patients who received lipiodol but remained in the hospital for a period less than two months were not included in the study.

Serial roentgenograms prior to and subsequent to bronchography were employed as the basis for the determination of changes occurring in the lung parenchyma of the patients with pulmonary tuberculosis under observation. The occurrence of new tuberculous lesions, reactivation in areas of retained iodized oil, reactivation of apparently stationary lesions, and bronchogenic spread were anticipated and, when noted, recorded and followed by means of subsequent serial roentgenograms.

The bronchography was performed following mild barbiturate sedation. The contrast medium used was lipiodol (Lafay), a poppyseed oil containing 40 per cent iodine. The lipiodol was instilled into the tracheobronchial tree through a catheter which had been passed nasally and guided fluoroscopically into the trachea after the preliminary spraying of the nose and pharynx with approximately 4 cc. of a 2 per cent solution of Pontocaine had been accomplished. The amount of the iodized oil that was instilled varied from 10 to 20 cc., the majority of patients receiving the latter amount. Bronchograms were taken immediately after the administration of lipiodol.

There was an immediate sharp rise in the blood iodine concentration following lipiodol bronchography in all patients. The pre-bronchography average blood

iodine concentration in the 49 patients with pulmonary tuberculosis was 12 γ per 100 ml., using the method at that time available.

TABLE 1

PRE- AND POST-BRONCHOGRAPHY; COLLAPSE THERAPY, BRONCHIECTASIS AND SPUTUM CONTENT OF TUBERCLE BACILLI

NUMBER OF PATIENTS	STAGE OF DISEASE	EXTENT OF DISEASE	COLLAPSE THERAPY PRIOR TO BRONCHOGRAPHY					SPUTUM PRIOR TO BRONCHOGRAPHY		BRONCHIECTASIS		COLLAPSE THERAPY SUBSEQUENT TO BRONCHOGRAPHY					
			Thoracoplasty	Pneumothorax	Oleothorax	Phrenic Crush and Pneumoperitoneum	None	Positive for *M. tuberculosis*	Negative for *M. tuberculosis*	Present	Absent	Thoracoplasty	Pneumothorax	Oleothorax	Phrenic Crush and Pneumoperitoneum	Pneumonectomy	None
49	Far advanced 34	Right lung only 7		1			6	3	4	4	3	3	2			1	1
		Left lung only 8				1	7	8	0	7	1	4			1	2	1
		Bilateral 19	3	1		2	13	17	2	15	4	11			2		6
	Moderately advanced 14	Right lung only 7		2		1	4	4	3	2	5	2	2				3
		Left lung only 4		1	2		1	2	2	2	2		1	2			1
		Bilateral 3				1	2	2	1	2	1		2		1		1
	Minimal 1	Left lung only 1					1	1		1							1
		Total	3	5	2	5	34	37	12	33	16	20	6	2	4	3	14

The maximum concentration of the blood iodine occurred within twenty-four hours following bronchography. The highest value obtained was 1,769 γ per 100 ml., while the average value was 765 γ per 100 ml. There was a gradual subsequent fall in the blood iodine concentration. After seven days the average values

were 183 γ per 100 ml. In thirty days the blood iodine concentration, as a rule, had returned to values within the normal range.

Clinical Material

In the group of 49 patients selected for the present study, 34 persons had far advanced pulmonary tuberculosis (table 1). In 19 patients the involvement was bilateral; in 7, the disease was limited to the right lung; in 8, to the left. Collapse therapy had been applied in 8 patients, and 26 had received no prior treatment. Bronchography performed during this study revealed bronchiectasis present in 26 patients. The bronchiectasis varied in degree from minimal bronchial dilatations to extensive sacculations. Following lipiodol bronchography, thoracoplasty collapse was applied in 18 patients, pneumoperitoneum combined with phrenic paralysis being used in 3. Of the 28 patients with sputum positive for tubercle bacilli prior to lipiodol bronchography, collapse therapy was applied to 22, with reversal of infectiousness in 15 patients. In 6 treated with bed rest alone, "conversion" of the sputum occurred in 3 patients. The sputum remained negative for tubercle bacilli in 6 patients, 2 of whom received collapse therapy.

There were 14 patients with moderately advanced tuberculosis (table 1). In 7 patients the involvement was limited to the right lung; in 4, to the left lung; while 3 had bilateral disease. In half of these patients, collapse therapy had been applied previously. Bronchography demonstrated the presence of bronchiectasis in 6 patients. Following the lipiodol bronchography, thoracoplasty collapse was used in 2 patients; pneumothorax, in 4; oleothorax, in 2; and pneumoperitoneum, in one. There were 8 patients with sputum positive for tubercle bacilli prior to bronchography. Collapse therapy "converted" 4 of these; while, of the 4 treated by bed rest alone, the sputum became negative for tubercle bacilli in 3. Of the 6 patients with sputum negative for *M. tuberculosis* prior to lipiodol instillation, 5 received, and one did not receive, collapse therapy following the use of the lipiodol; the sputum remained negative for tubercle bacilli in all of the cases.

One patient had minimal tuberculosis. She had involvement of the left lung only and had not received previous collapse therapy. The sputum was negative for tubercle bacilli. A guinea pig injected with bronchoscopically obtained secretions from the left main bronchus developed tuberculosis. Minimal bronchiectasis was present in the lingula of the patient's left upper lobe. No collapse therapy was given following the use of lipiodol, and the sputum remained negative for tubercle bacilli in spite of an episode of acute iodism which occurred on the ninth day following lipiodol bronchography.

OBSERVATIONS

For purposes of description, the 49 patients studied were divided into three groups (table 2). There were 22 patients in *Group I*. These had been adequately studied by serial roentgenography prior to the instillation of lipiodol, and it was ascertained that bronchogenic spread of disease had not occurred for some time. *Group II* consisted of 22 patients who had only an admission roentgenogram

prior to the use of lipiodol and, hence, the spreading tendency of the underlying pulmonary tuberculous lesions was not determined at the time of lipiodol bron-

TABLE 2

INCIDENCE OF "POSITIVE" SPUTUM, CAVITATION, BRONCHIECTASIS, AND BRONCHOGENIC SPREAD OF DISEASE

GROUP	SUBGROUP	SPUTUM CONTENT OF TUBERCLE BACILLI				PULMONARY CAVITY				BRONCHIECTASIS			
		Positive		Negative		Present		Absent		Present		Absent	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
I No bronchogenic spread of disease occurred before or after bronchography 22 patients (45 per cent)		15	68	7	32	14	64	8	36	15	68	7	32
II Bronchogenic spread of disease before bronchography was not determined. 22 patients (45 per cent)	A "Spread" did not occur following bronchography. 18 patients (82 per cent)	12	67	6	33	16	89	2	11	12	67	6	33
	B "Spread" occurred following bronchography from causes not due to lipiodol. 4 patients (18 per cent)	4	100			3	75	1	25	3	75	1	25
III Bronchogenic spread of disease was noted prior to bronchography. 5 patients (10 per cent)	A "Spread" occurred following bronchography. 3 patients (60 per cent)	3	100			2	67	1	38	3	100		
	B "Spread" did not occur following bronchography. 2 patients (40 per cent)	2	100			2	100			1	50	1	50

chography. The 5 patients of *Group III* were studied adequately by serial roentgenograms and showed pre-lipiodol bronchogenic spread of disease, further evidence that the tuberculous infection was progressive.

Resistance and Bronchogenic Spread of Disease Following Bronchography

Twenty-two patients of *Group I* were found on serial roentgenography to have pulmonary tuberculous lesions which had not progressed for a period of at least six months or, if the pre-bronchography period of study were shorter, which showed evidence of regression. Fourteen of these patients had far advanced, 7 had moderately advanced, and one had minimal, pulmonary tuberculosis. No post-lipiodol bronchogenic spread of disease was observed in any of these patients during the period of study.

Twenty-two patients of *Group II* had lipiodol bronchography shortly after admission to the hospital. Since only the admission film was available, no decision could be reached concerning the spreading tendency of the underlying tuberculous lesions.

No post-lipiodol spread of disease was observed in the 18 patients comprising *Group II A*. Fourteen had far advanced pulmonary tuberculosis, and 4 had moderately advanced tuberculosis.

In *Group II B*, bronchogenic spread of disease occurred during the post-bronchography period in 4 patients, but from causes which were not considered to have been due to lipiodol. These 4 cases are presented in the following protocols.

M. M., a 17-year-old white female, was admitted to the Franklin County Tuberculosis Hospital on January 14, 1946, with the diagnosis of far advanced pulmonary tuberculosis. The left lung showed marked destruction with multiple large cavities and caseation. The right lung was clear. The sputum was positive for tubercle bacilli. Bronchiectasis of the left lower lobe was demonstrated by bronchography on January 30, 1946. A left pneumonectomy was performed on February 26, 1946, but tuberculous empyema, bronchopleural fistula, and bronchogenic spread of disease developed, and the patient died on April 14, 1946. Autopsy revealed left tuberculous pleuritis, mediastinitis and pericarditis, bronchopleural fistula, and tuberculous pneumonia of the right middle and lower lobes.

Comment: The post-lipiodol spread of disease in this patient occurred due to complications following pneumonectomy, performed at a time when antibiotics were not in use at the hospital.

D. Q., a 44-year-old white female, was admitted to the hospital on December 26, 1945 with far advanced pulmonary tuberculosis. Infiltration was present in the left upper and lower lobes, and a large cavity was seen opposite the left hilum. The right lung was clear. The sputum was positive for tubercle bacilli. Bronchography on January 2, 1946 revealed bronchiectasis of the left lower lobe in addition to the large cavity. A left pneumonectomy was performed on January 24, 1946. The patient developed a bronchopleural fistula, however, and died on July 18, 1946 from tuberculous pneumonia of the right lung.

Comment: The bronchogenic spread of disease in this patient occurred due to the complications following a pneumonectomy.

G. H. W., a 42-year-old white male, was admitted to the hospital on January 7, 1946 with far advanced pulmonary tuberculosis. Marked destruction of the right lung had occurred. A 4 by 5 cm. cavity was present in the upper lobe, a 2 by 3 cm. cavity in the lower lobe, and caseating lesions were found in the remaining portions of the right lung. Infiltration was present in the middle third of the left lung. The sputum contained an abundance of tubercle bacilli. Bronchiectasis was demonstrated in all lobes; on the right, by bronchog-

raphy on January 16, 1946. On February 18, 1946 the patient developed a severe pulmonary hemorrhage with subsequent marked bronchogenic spread to the left lung, with progression of the tuberculous infection.

Comment: The bronchogenic spread of disease in this patient followed a severe pulmonary hemorrhage.

G. M., a 62-year-old white female, was admitted to the Franklin County Tuberculosis Hospital on July 16, 1946 with moderately advanced pulmonary tuberculosis. The lower half of the right lung field was involved in an exudative productive process which extended from the hilum to the periphery and to the base. The left lung was normal. Bronchoscopy revealed extensive tuberculous ulceration of the right main bronchus, with edema and narrowing of the orifice of the right middle lobe. No bronchiectasis was seen on lipiodol bronchography on August 14, 1946. A roentgenogram of October 12, 1946 showed no spread of the tuberculous lesion. Bronchoscopic treatment of the tuberculous bronchial ulcers with silver nitrate was performed on October 24, 1946 and December 12, 1946. Much bleeding occurred from the ulcer area following the latter attempt. Six weeks later, January 22, 1947, marked infiltration was seen in the right hilar region, in the peripheral portion of the middle third of the right lung, and in the *left* lower lobe. This infiltration cleared on bed rest alone, with eventual discharge of the patient with apparently arrested tuberculosis.

Comment: This bronchogenic spread of disease resulted following bronchoscopically induced moderate hemorrhage from a tuberculous ulcer.

The 5 patients comprising *Group III* were studied by serial roentgenography, and all were found to have had bronchogenic spread of their tuberculosis *prior* to lipiodol bronchography.

Bronchogenic spread of disease in the post-lipiodol period was observed in 3 patients of *Group III A*, 2 of whom had far advanced pulmonary tuberculosis and the other had moderately advanced tuberculosis. The case records are herewith presented.

P. W., a 32-year-old white woman, was admitted to the Franklin County Tuberculosis Hospital on December 7, 1945 with bilateral far advanced pulmonary tuberculosis. Extensive caseation was present in the upper and lower lobes on the right. A large cavity was present in the right upper lobe and another in the right hilar region. The left lung showed infiltration in its middle third. A right pneumothorax was instituted on January 11, 1946; it was discontinued, however, when the cavity in the right apex began to "balloon" out. The disease was progressive on the right. Marked bronchiectasis was noted in the right lower lobe by bronchography on February 6, 1946. On March 29, 1946, seven weeks later, a chest film revealed a 6 by 8 cm. tension cavity in the right apex and evidence of extensive spread of the disease to the left lung. In late March, tuberculous laryngitis and enteritis developed. The patient died on April 28, 1946 from tuberculous peritonitis following the perforation of a tuberculous intestinal ulcer. Autopsy revealed a tuberculous enterocolitis which involved most of the jejunum, all of the ileum, and all of the colon up to the sigmoid. Large oval ulcers were present in these areas, and tuberculous peritonitis had resulted from the perforation of such an ulcer near the terminal ileum. Tuberculous tracheitis and hematogenous tuberculosis of the spleen and liver were also noted.

Comment: Bronchogenic spread of disease occurred seven weeks following the use of lipiodol in a patient with progressive overwhelming pulmonary tuberculosis.

C. L. C., a 26-year-old Negro female, was admitted to the hospital on February 8, 1945 with far advanced pulmonary tuberculosis. A large cavity was present in the left upper lobe,

while caseous pneumonic lesions involved the remainder of the left lung. The right lung was clear. A left pneumothorax, started on February 20, 1945, was abandoned because of apical symphysis. A subsequently instituted left phrenic crush and pneumoperitoneum had to be abandoned when the cavity in the left upper lobe became larger. The disease was rapidly progressive on the left. On November 9, 1945, the cavity on the left had so enlarged that it occupied nearly all of the apex, while the caseous pneumonic lesions involving the remainder of the lung had increased. The sputum contained many tubercle bacilli. Bronchiectasis of the left lower lobe was demonstrated on lipiodol bronchography December 12, 1945. Two months following lipiodol bronchography, bronchogenic spread to the periphery of the middle third of the right lung was demonstrated by roentgenography. This lesion slowly regressed. In August, 1946, a lemon-sized dense infiltrative lesion appeared in the right hilar region. The cavity on the left was found to be larger. In November, 1946, a further spread of disease was noted in the right lung. A pneumoperitoneum, and later a right pneumothorax, failed to prevent further extension of the lesions on the right.

Comment: Bronchogenic spread of disease occurred eight weeks following the use of lipiodol in a patient with progressive tuberculosis.

C. R. B., a 55-year-old Negro male, was admitted to the hospital on July 8, 1946 with moderately advanced pulmonary tuberculosis. A pre-admission chest roentgenogram on June 13, 1946 revealed infiltration and mottling in the right lower lobe and infiltration in the right apex and in the first interspace anteriorly. The admission roentgenogram on July 9, 1946 revealed that the disease in the right lower lobe had progressed, but that the infiltrative lesions in the right apex and first interspace had cleared. Bronchoscopy revealed marked stenosis of the right lower lobe bronchus and evidence of endobronchial disease. Bronchiectasis of the right middle and lower lobes was demonstrated by lipiodol bronchography on August 8, 1946. The patient was considered to be a poor surgical risk, both because of lowered vitality and because of a markedly enlarged heart. On September 19, 1946, six weeks after the instillation of lipiodol, bronchogenic spread to the right apex was noted. On December 11, 1946, spread to the right first interspace anteriorly was noted. The disease continued to progress, eventually involving both lungs and causing the patient's death on April 18, 1947.

Comment: Bronchogenic spread of disease occurred six weeks after the use of lipiodol in a patient with progressive tuberculosis.

No post-lipiodol bronchogenic spread of disease due to lipiodol or to the procedure of the instillation of lipiodol was noted in 2 patients comprising *Group III B* who had bronchogenic spread of disease prior to the use of lipiodol.

R. C. P., a 42-year-old white male, was admitted on November 24, 1945 with pulmonary tuberculosis (table 2, *Group II B*) involving only the right lung. Comparison of the admission film with preadmission films revealed that the disease on the right was progressive. The sputum was positive for tubercle bacilli. No bronchiectasis was seen on lipiodol bronchography on December 10, 1945. The disease on the right showed some extension, but no spread to either the right or left lung was noted during the next four months. Following the first stage of thoracoplasty on the right in April, 1946, bronchogenic spread of disease to the left lung occurred and an area of infiltration appeared at the hilum on the left. This infiltration regressed sufficiently to permit the completion of the thoracoplasty in June, 1946. The sputum "converted" and no further bronchogenic spread occurred, but a gradual extension of the infiltrative lesions at the left hilum has been noted, and the left lower lobe has become involved in the infiltrative process.

Comment: The bronchogenic spread of disease occurring four months after the use of lipiodol was due to the manipulations during surgery. The delicate balance between resistance and infection is quite evident in this patient.

A. B., a 24-year-old Negro female, was admitted to the hospital on September 27, 1946 with moderately advanced pulmonary tuberculosis. Both apices contained mottled areas, more extensive on the left, and multiple areas of decreased density. The sputum was positive for tubercle bacilli. Shortly after admission, spread to the left lower lobe occurred. Minimal bronchiectasis in the left lower lobe was noted by lipiodol bronchography on October 16, 1946. A left pneumothorax was started on November 6, 1946, and the sputum "converted." The sputum became positive for tubercle bacilli again on January 8, 1947 but an increase in the amount of pneumothorax refills on the left "converted" it again. On February 11, 1947, an increase in the infiltrative lesions in the left right interspace was noted and a right pneumothorax was started. Under the regimen of bilateral pneumothorax, progressive improvement of the lesions on the right and left have been noted.

Comment: No post-lipiodol bronchogenic spread of disease occurred in a patient with obviously poor resistance. Collapse therapy prevented progression of the disease.

General Comment

Patients who have developed a degree of resistance sufficient to prevent the spread of tuberculosis prior to lipiodol bronchography will demonstrate little, if any, tendency to develop bronchogenic spread during the post-lipiodol period. The writers believe that lipiodol bronchography for these patients is without any particular danger. Patients with poor resistance and with evidence of pre-lipiodol bronchogenic spread of disease will have a tendency to develop bronchogenic spread following the instillation of lipiodol, unless the patient is aided by adequate collapse therapy in the pre-lipiodol, or in the immediate post-lipiodol, period.

Sputum Positive for M. Tuberculosis and Subsequent Bronchogenic Spread of Disease Following Bronchography (Table 2)

Of the 22 patients comprising *Group I*, 15 had sputum positive for *M. tuberculosis* and in 7 the examinations were negative. No bronchogenic spread of disease occurred in any of these patients following bronchography.

Of the patients in *Group II A*, 12 had positive and 6 had negative examinations of the sputum for *M. tuberculosis*. No bronchogenic spread of disease occurred in any of these patients during the four-month period following bronchography.

Of the patients in *Group II B*, all 4 had sputum positive for tubercle bacilli and all 4 had post-lipiodol bronchogenic spread of disease. The exacerbations were not considered to have been related to the lipiodol procedure.

All 3 patients of *Group III A* had sputum positive for tubercle bacilli and experienced bronchogenic spread of disease during the period following bronchography.

Both patients in *Group III B* had sputum positive for *M. tuberculosis*, yet bronchogenic spread of disease due to lipiodol bronchography did not occur.

Summarizing the above results, it may be seen that all 8 patients who had bronchogenic spread of disease during the period following bronchography from whatever cause had a sputum positive for tubercle bacilli at the time lipiodol was instilled. Of the 41 patients who did not experience post-lipiodol bronchogenic

spread of disease, tubercle bacilli were present in the sputum of 29 and absent from the sputum of 12.

Comment: Post-lipiodol bronchogenic spread of tuberculosis does not occur in patients whose sputum is negative for tubercle bacilli, while the presence of bacilli in the sputum at the time of lipiodol instillation does not necessarily mean that bronchogenic spread of disease will occur following the use of lipiodol.

Pulmonary Cavitation and Subsequent Bronchogenic Spread of Disease Following Bronchography

Of the 22 patients in *Group I* (table 2), 14 had demonstrable pulmonary cavitation and 8 had no cavity. No post-lipiodol spread of disease occured in any of these patients.

Of the 18 patients in *Group II A*, 16 had demonstrable pulmonary cavitation and 2 had no caivty. No post-lipiodol spread of disease occurred in any of these patients.

Of the 4 patients in *Group II B*, 3 had pulmonary cavitation and one had no cavity. Post-lipiodol bronchogenic spread occurred in all 4, due to complications of surgery and also recent hemorrhage.

Of the 3 patients in *Group III A*, 2 had pulmonary cavitation and one had no cavity. Bronchogenic spread of disease followed lipiodol instillation.

Both patients of *Group III B* had pulmonary cavitation. Neither patient had bronchogenic spread of disease due to lipiodol. One patient had a bronchogenic spread of disease following the first stage of a thoracoplasty.

Definite pulmonary cavitation was present in 37 of the 49 patients studied. Of these, 31 did not show a post-lipiodol bronchogenic spread of disease, while 6 developed bronchogenic spread, possibly from the lipiodol procedure but more probably as a result of the complication of pulmonary tuberculosis combined with operative procedures. Of the 12 patients who did not have a pulmonary cavity, no bronchogenic spread occurred in 10, while 2 showed subsequent progression of the lesion.

It is concluded from these results that the presence of a pulmonary cavity does not necessarily mean that bronchogenic spread will occur following the use of lipiodol.

Bronchiectasis and Subsequent Spread Following Bronchography (Table 2)

Of the 22 patients in *Group I*, bronchiectasis was present in 15. Of the 18 patients in *Group II A* and of the 4 patients in *Group II B*, 2 had bronchiectasis. All 3 patients of *Group III A* and one of the 2 patients in *Group III B* had bronchiectasis.

In 41 patients without bronchogenic spread of disease during the period following lipiodol bronchography, 28 also had bronchiectasis. Of the 8 patients who developed post-lipiodol bronchogenic spread from the lipiodol procedure or from complications, 6 had bronchiectasis.

It appears that the presence of bronchiectasis does not necessarily mean that bronchogenic spread will occur following the instillation of lipiodol.

Collapse Therapy and Subsequent Bronchogenic Spread Following Bronchography (Table 1)

Pre-bronchography collapse therapy: Collapse therapy was applied in 15 patients previous to bronchography, while in 34 patients such procedure was not used. Of the 15 patients with pre-bronchography collapse, the sputum became negative for tubercle bacilli in only 6. Of the 9 patients with a residual "positive" sputum, 2 showed pre-lipiodol bronchogenic spread of disease. Of the 34 patients who had not received pre-lipiodol collapse, only one experienced bronchogenic spread of disease.

Post-bronchography collapse therapy: Thirty-four patients received, and 14 patients did not receive, post-lipiodol collapse therapy. Of the former, 24 had positive and 10 had negative examinations of the sputum for tubercle bacilli. Collapse therapy in the patients with the sputum positive for tubercle bacilli was performed within one month after the lipiodol instillation in 16 patients, within two months in 3, within three months in 3, within four months in 2, and within five months in one. The sputum of 18 of the 25 patients who received collapse therapy was converted to "negative."

Concerning the 3 patients of *Group III A*, who demonstrated both pre-lipiodol and post-lipiodol bronchogenic spread of disease, one received an inadequate pneumoperitoneum and the other 2 received bed rest only. One patient who had experienced pre-lipiodol bronchogenic spread of disease had no post-lipiodol bronchogenic spread of disease, a pneumothorax having been instituted early in the post-lipiodol period.

An adequate pre-lipiodol or early post-lipiodol collapse will tend to prevent post-lipiodol bronchogenic spread of tuberculosis. A patient with roentgenographically indicated poor resistance will tend to have pre-lipiodol, as well as post-lipiodol, spread of disease unless aided by adequate collapse measures.

The Retention of Lipiodol and Subsequent Bronchogenic Spread of Disease

In 13 patients, the lipiodol disappeared from the lungs within a period of six months, as demonstrated by later roentgenograms. In the remaining 36 patients, lipiodol still remained in the lungs at the time the study was completed, at the time patients were separated from the hospital, or at the time of death.

At no time was any local reaction attributable to the residual lipiodol observed in any of the patients. Patient G. M. developed bronchogenic spread of disease and infiltrative reactions in both the right and left lungs four months after lipiodol instillation and six weeks after a previous hemorrhage from a tuberculous bronchial ulcer induced during attempts at bronchoscopic treatment. The reaction on the right occurred around areas of retained lipiodol, but the reaction on the left took place in areas which were free of lipiodol. The areas on the left, which still had lipiodol in them, were not involved in the infiltrative process. Careful pathologic study demonstrated that the bilateral infiltrative reaction appeared to occur independently of the retained lipiodol.

The retention of lipiodol for various periods of time appears to play no part

in the activation of pulmonary tuberculous lesions during the bronchogenic spread of tuberculosis, and does not appear to exert any local deleterious effect on the surrounding pulmonary parenchyma.

Acute Iodism and the Subsequent Spread of Pulmonary Tuberculosis

Acute iodism was encountered in one patient with minimal pulmonary tuberculosis of the left lung. The following is a brief summary of the pertinent case history.

M. J., a 48-year-old white woman, was admitted to the Franklin County Tuberculosis Hospital on September 5, 1946. Roentgenograms on admission revealed slight infiltration in the first interspace anteriorly of the left lung and in the region of the lingula. The right lung was clear. The sputum was negative for tubercle bacilli, but guinea pig inoculation of bronchoscopically obtained secretions from the left bronchus revealed a tuberculous infection. A superficial ulcer in the region of the bifurcation of the left upper lobe bronchus was found on bronchoscopy on October 5, 1946. Minimal bronchiectasis of the left upper lobe was demonstrated by lipiodol bronchography on October 7, 1946. On October 16, 1946, the patient developed chills and fever. On the next day a maculopapular rash appeared on the chest, back, and arms. Edema of the face, legs, arms, and lungs developed early and became worse during subsequent days. The conjunctiva of both eyes and the mucous membranes of both nostrils were injected.

Rales in both lungs were heard on the tenth post-lipiodol day. They became more abundant as the reaction developed. A chest roentgenogram of October 21, 1946, on the fourteenth post-lipiodol day, revealed infiltration and increased haziness of the left apex with an increase in the original area of apical infiltration. Increased haziness was also present in the left lower lobe. The right lung revealed areas of infiltration in the first and second interspaces and hazy infiltration of the right middle and lower lobes. A roentgenogram obtained on October 29, 1946, the twenty-second post-lipiodol day, revealed a clearing of all areas of infiltration except in the left apex, where the original area of infiltration persisted but had not extended. A film obtained thirteen weeks later revealed no progression of the lesion in the left apex, and no new lesions in any portion of the remaining lung fields became evident. Roentgenographic examination in April, 1947, revealed that the lesions in the left apex and first interspace had undergone definite regression.

The total blood iodine concentration, determined on October 18, 1946, eleven days after lipiodol instillation and two days after the onset of the reaction, was 511 γ per 100 ml. This value was 2.44 times higher than the average total blood iodine concentration found on the seventh day following bronchography in an extensive study of patients with pulmonary tuberculosis. It appears, therefore, that acute iodism does not seem to cause extension or spread of pulmonary tuberculosis lesions.

SUMMARY

The effect of the intratracheal instillation of lipiodol on the subsequent course of pulmonary tuberculosis was studied in 34 patients with far advanced, 14 patients with moderately advanced, and one with minimal, tuberculosis.

Bronchogenic spread of disease following lipiodol bronchography can occur in patients with sputum positive for tubercle bacilli and with roentgenographically demonstrable unstable progressive lesions.

Bronchogenic spread of disease following bronchography does not occur in patients who demonstrate roentgenographically a favorable resistance-infection relationship during the period prior to bronchography.

The retention of lipiodol in the bronchopulmonary tissues as well as the occurrence of acute iodism does not appear to have an unfavorable effect on the subsequent course of pulmonary tuberculosis.

The presence of sputum positive for tubercle bacilli, pulmonary cavity, and of bronchiectasis does not necessarily indicate that bronchogenic spread of disease will subsequently occur following lipiodol bronchography.

Iodized oil bronchography is a safe procedure in patients with controlled, stable, or regressive pulmonary tuberculous lesions.

SUMARIO

Efecto de la Broncografía con Aceite Yodado sobre la Evolución Subsiguiente de la Tuberculosis Pulmonar

Ef efecto de la instilación intratraqueal de lipiodol sobre la subsiguiente evolución de la tuberculosis pulmonar fué estudiado en 34 enfermos con casos muy avanzados, 14 con casos moderamente avanzados y uno con lesiones mínimas.

Puede ocurrir difusión broncógena a continuación de la broncografía lipiodal en sujetos con esputo positivo para bacilos tuberculosos y con lesiones evolutivas inestables, radio gráficamente observables.

No ocurre difusión broncógena consecutivamente a la broncografía en enfermos que muestran radiográficamente una favorable relación de resistencia-infección durante el período anterior a la broncografía.

La retención de lipiodol en los tejidos broncopulmonares así como la ocurrencia de yodismo agudo no parece ejercer efecto desfavorable sobre la evolución subsiguiente de la tuberculosis pulmonar.

La presencia de esputo positivo para bacilos tuberculosos, de cavernas pulmonares y de bronquiectasia no denota forzosamente que habrá difusión broncógena consecutivamente a la broncografía lipiodal.

La broncografía con aceite yodado es un procedimiento inocuo en los pacientes con lesiones tuberculosas cohibidas, estables o regresivas en el pulmón.

RESUME

L'action de la bronchographie à l'huile iodée sur l'évolution ultérieure de la tuberculose pulmonaire

L'influence de l'instillation intratrachéale de lipiodol sur l'évolution ultérieure de la tuberculose pulmonaire à été étudiée chez 34 malades présentant une tuberculose très avancée, chez 14 malades présentant une tuberculose modérément avancée et chez un malade présentant des lésions minimes.

La dissémination bronchogène succédant à la bronchographie peut se produire chez des tuberculeux avec crachats positifs et lésions évolutives démontrables par la radiographie.

La dissémination bronchogène succédant à la bronchographie ne se produit pas chez les malades pour lesquels l'examen radiologique fournit la preuve d'un équilibre résistance-infection favorable.

La rétention de lipiodol dans les tissus broncho-pulmonaires, de même que les accidents d'intolérance à l'iode, ne semblent pas avoir une action défavorable sur le cours ultérieur de la tuberculose pulmonaire.

La présence de crachats BK-positifs, de spélonques et de bronchiectasie n'indique pas nécessairement qu'une dissémination bronchogène succédera à la bronchographie au lipiodol.

La bronchographie à l'huile iodée représente un procédé sans danger chez le tuberculeux dont les lésions sont contrôlées, stabilisées ou régressives.

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A METHOD FOR PRODUCING TUBERCULOUS MENINGITIS IN GUINEA PIGS BY LUMBAR INTRATHECAL INOCULATION[1]

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(Received for publication July 28, 1952)

INTRODUCTION

The method to be described in the present report was developed in order to obtain reproducible disease for studies on the pathogenesis and the chemotherapy of experimental tuberculous meningitis in guinea pigs. The tuberculous encephalitis that may be readily produced in these animals by intracerebral inoculation is accompanied by meningitis (1), and this means of producing the disease for therapeutic studies has been used by some workers (2, 3). It was considered desirable, however, to use an approach that would not primarily violate the brain. The suboccipital route of inoculation devised in 1898 by Martin (4) was not attempted because he, as well as other investigators, had reported that the procedure was a difficult one in guinea pigs and was accompanied by high initial mortality.[3]

In the present study, lumbar intrathecal inoculation was found to be a satisfactory method for producing severe tuberculous meningitis without much difficulty and without a high initial mortality.

METHODS

Technique of procedure: Large guinea pigs weighing 600 to 800 gm. were selected although, with practice, smaller animals may be used. Anesthesia was not necessary since the procedure appeared to produce little discomfort to the animal. The guinea pig was restrained by an assistant who held the hind limbs gently, but firmly, between the thumb and forefinger as shown in figure 1. Gentleness is important because the animal will struggle against the restraint but does not greatly resist the insertion of the needle.

An area over the lumbar region was clipped and cleaned with 70 per cent alcohol. The most posterior interspinal space which could be palpated was chosen. This space is between the fifth and sixth lumbar vertebrae and measures approximately 4 to 5 mm. in width. A short (2.5 cm.) 21-gauge (0.8 mm.) needle was inserted at an angle of 45 degrees with the sacrum. A bony resistance is felt at a depth of 10 to 15 mm. The lower roentgenogram in figure 2 shows the position of the needle. With a tuberculin syringe, 0.02 ml. of air was rapidly injected. An immediate slight jerk of both hind limbs indicated that the needle was in the proper position. If this typical reaction was observed, 0.1 ml. of a suspension of tubercle bacilli in physiologic salt solution was injected slowly. The needle was then withdrawn, and the area was wiped with 70 per cent alcohol.

If there was no immediate response to the injection of 0.02 ml. of air, the needle was withdrawn slightly and again inserted, care being taken to direct the needle toward the

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[3] A review of the literature up to 1935 on experimental tuberculous meningitis is given by Boquet and Broca (5).

center of the vertebral canal. No infecting inoculum was injected into animals in which the characteristic slight extension of the legs could not be elicited.

Mortality from the procedure: In the early trials, the injection of larger amounts of air, 0.1 to 0.5 ml., caused either immediate death, due to respiratory failure, or paraplegia, with death occurring up to five days later. When the amount of air was reduced to 0.02 ml. and followed by injection of 0.1 ml. of bacterial suspension, however, immediate death occurred in only 2 of the 150 animals used in subsequent experiments. The injection of air appeared to be more dangerous than the injection of bacterial suspensions.

FIG. 1. Lumbar intrathecal inoculation of guinea pigs. The animal is restrained by an assistant holding the hind limbs gently, but firmly, between the thumb and forefinger with the hands resting on the table top. An area over the lumbar vertebrae is clipped and cleaned with 70 per cent alcohol. A 21-gauge hypodermic needle (0.8 mm. in diameter) 2.5 cm. long is inserted at an angle of 45 degrees into the most posterior interspinal space that can be palpated. This is between the fifth and sixth lumbar vertebrae. The space is approximately 4 mm. wide. The needle is inserted until a bony resistance is felt, which is usually at a depth of 10 to 15 mm. No anesthesia is required since there is apparently little discomfort to the animal.

Occasionally, paralysis of the hind limbs, predominantly unilateral, was seen after injection of the suspension of tubercle bacilli. This appeared to be due to trauma of the spinal cord. The paralysis usually disappeared within a few days. This complication was most frequent in the animals which appeared to react to pain when the needle was inserted. It could be prevented by changing the direction of the needle.

Preparation of inoculum: For the studies reported here, the infecting inoculum was prepared from a five-day old growth of the H37Rv strain of tubercle bacilli cultivated in modified Proskauer and Beck liquid medium (6) containing 0.2 per cent Tween 80.[1] This provided a well-dispersed suspension of bacterial units, of which 90 per cent contained only 1 to 4 bacilli. The remainder consisted of clumps which contained 5 to 20 bacilli. The number of bacilli per unit volume of medium was determined by means of a Petroff-Hausser counting

[1] Tween 80 is the proprietary name for the polyoxyethylene derivative of Sorbitan monooleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

chamber. Dilutions of the culture were made with sterile physiologic salt solution to obtain the desired number of bacilli per 0.1 ml. Bacterial susp. .sions were made immediately before use.

Animal experiment: One of the first experiments to be done will be described to show the effect of various amounts of inoculum on incubation period and survival time plus the necropsy and histopathologic appearance of the meningitis. Four groups of 8 animals each, as shown in table 1, were used. For each animal

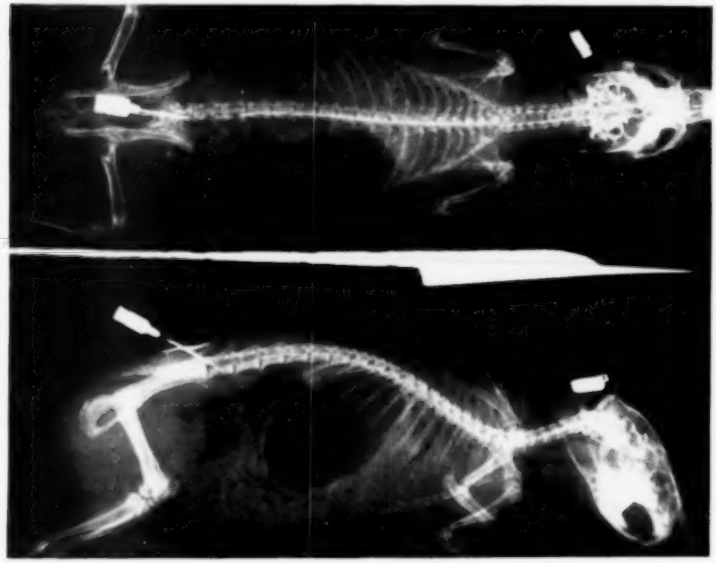

FIG. 2. The lower roentgenogram shows the position of the needle inserted between the fifth and sixth lumbar vertebrae until the body of the fifth lumbar vertebra is reached. The upper picture was taken after the injection of 0.5 ml. of lipiodol, which is seen as a thin white line. This amount of lipiodol was used for better delineation. The injection of 0.1 ml. resulted in a similar but less pronounced shadow. (The needle in the upper picture has been dislodged. The point should be in the center of the vertebral canal.) Half natural size.

in the first three groups, the inoculum was 0.1 ml. of suspension containing, respectively, 10,000, 100,000, and 1,000,000 tubercle bacilli and was given intrathecally. In those in the fourth group, 0.1 ml. of a suspension containing 1,000,000 bacilli was injected subcutaneously over the sternum. One animal in the first group died in 3 days and 2 died in the third group after one and 3 days, respectively. These were discarded. None of the other animals had symptoms indicating any injury of the cord as a result of the procedure. When animals died, the brain was removed and preserved for histopathologic studies. The entire vertebral column was placed in 10 per cent neutral formalin solution, and the

cord was removed when fixation was complete. Portions of the lungs, liver, and spleen also were preserved for sectioning.

RESULTS

Incubation period: After 7 to 10 days of infection, the animals given 1,000,000 tubercle bacilli intrathecally began to show signs of illness. Weakness of the hind limbs, roughening of the hair, lassitude, and loss of appetite were noted. For those which received injections of 100,000 or 10,000 bacilli, the average incubation

TABLE 1

EFFECT OF INTRATHECAL INOCULATION OF GUINEA PIGS WITH VIRULENT TUBERCLE BACILLI

GROUP	SIZE OF INOCULUM*	NUMBER OF ANIMALS	FIRST APPEARANCE OF SYMPTOMS, DAYS		SURVIVAL TIME, IN DAYS		TUBERCULIN REACTION IN 15 DAYS		AVERAGE CHANGE OF WEIGHT IN 15 DAYS
			Range	Average	Range	Average	Positive	Negative	
1	10,000	7†	15 to 18	16.7	15 to 31‡	24.3	1	6	−5 gm. (−110 gm. in 20 days)
2	100,000	8§	12 to 15	13.4	13 to 20	17.4	0	7	−210 gm.
3	1,000,000	6†	7 to 10	9.2	9 to 14	11.3	No survivors in 15 days		(−50 gm. in 8 days)
4	1,000,000 (subcutaneously)	8§					8	0	+35 gm.

* Approximate number of bacilli in 0.1 ml. of suspension.

† One animal in the first group and 2 animals in the third group died within five days and were discarded.

‡ One animal (tuberculin positive in 15 days) had symptoms on the eighteenth day but did not die. This animal is not included in the data for survival time.

§ One animal died with lesions of generalized tuberculosis on the one hundred and thirty-eighth day. The others were killed on the one hundred and sixty-first day and were found to have generalized tuberculosis.

The tuberculin tests were done with 0.1 ml. of 1:100 Old Tuberculin injected intracutaneously.

period was 13.4 and 16.7 days, respectively. These data are presented in table 1. None of the animals in which 1,000,000 tubercle bacilli were injected subcutaneously had similar symptoms.

Symptoms: The severity of the symptoms increased noticeably within a few days after onset, regardless of the incubation period. The animals failed to eat, and loss of weight was pronounced. The weakness of the hind limbs progressed rapidly to complete posterior paralysis within a few days. The abdominal muscles became flaccid. This was accompanied in most animals by urinary and fecal incontinence. In several animals in each group, paralysis of one or both fore limbs developed, and a number had opisthotonos in the late stages of the disease.

Survival time: Referring to the data recorded in table 1, it may be seen that the

average survival time appeared to be related to the size of the infecting inoculum. In the animals infected with 1,000,000 bacilli, death occurred in 9 to 14 days after injection. The average duration of noticeable illness in this group was only 2.1 days. All the guinea pigs given 100,000 bacilli died in 13 to 20 days after inoculation, the average duration of life being 4 days after the onset of symptoms.

Infection with 10,000 tubercle bacilli caused a less rapidly fatal disease. In the group inoculated with 10,000 bacilli, with one exception, the deaths were spread over a period of 15 to 31 days after infection, and the average duration of symptoms was 7.6 days preceding death. The one exception in this group was an

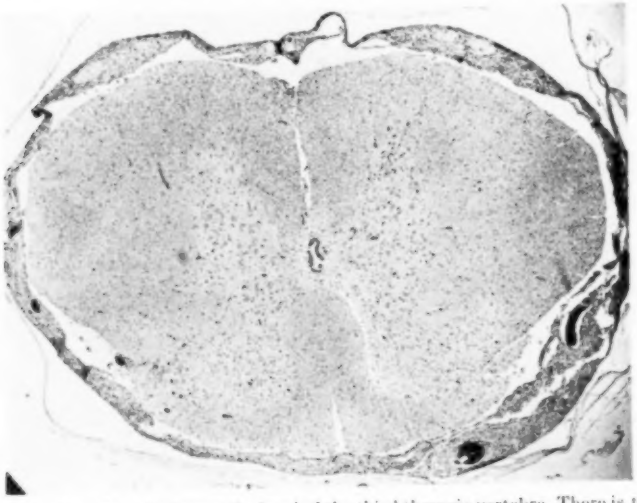

FIG. 3. Section of cord taken at the level of the third thoracic vertebra. There is thickening of the meninges around the entire cord due to the presence of mononuclear cells. This section was obtained from a guinea pig which died thirteen days after intrathecal inoculation with 1,000,000 tubercle bacilli. (Hematoxylin and eosin stain. × 40)

animal in which early symptoms developed on the eighteenth day of infection. Loss in weight and paralysis of the posterior limbs were noted. The animal was able to eat, however, and gradually regained weight within 3 weeks. The paralysis persisted for 33 days, after which the animal was normal in appearance for 44 days. It then started to lose weight again, and the paralysis reappeared. The animal became progressively weaker but survived for an additional 46 days. This animal is of interest because it is the only one of the animals inoculated intrathecally which was found to be sensitive to tuberculin when tested 14 days after infection (table 1).

Tuberculin tests: Forty-eight hours prior to infection, all animals in the experiment were tested with 0.1 ml. of 1:100 dilution of Old Tuberculin given intracutaneously. None of the animals reacted to tuberculin. After 15 days of infec-

tion, all surviving animals were tested again. Each of the animals in which 1,000,000 bacilli had been injected subcutaneously reacted positively. As mentioned previously, only one of those infected intrathecally gave a positive reaction. This animal outlived by many weeks the other animals in its group.

Post-mortem observations: Gross examination of the brains revealed only pronounced congestion. Only one animal had hydrocephalus, which was slight. Similarly, in the spinal cord there were no other significant changes. In the

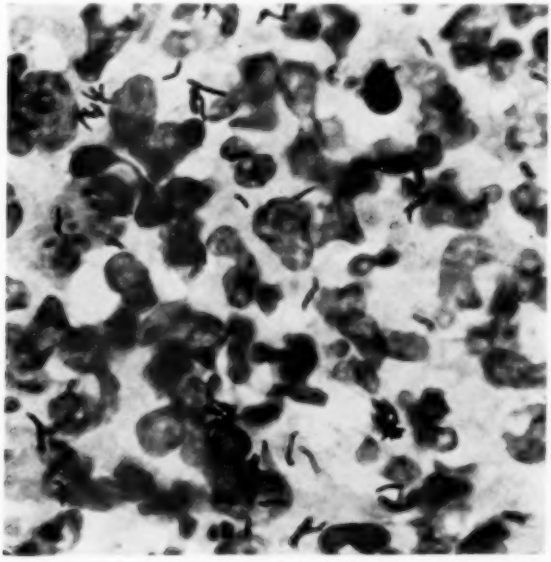

FIG. 4. Exudate involving the meninges of the brain. The cellular reaction, composed largely of histiocytes was characteristic of the meningeal lesions in all of the animals. The tissue was stained for acid-fast bacilli which were found to be largely extracellular. The section was taken from the middle of the cerebrum of an animal that died twenty days after intrathecal injection of 100,000 tubercle bacilli. (Hematoxylin-carbol-fuchsin stain. × 1,800.)

animals which died within the first several weeks of infection, enlargement of the spleen and also a few miliary lesions in the spleen and liver were observed. In addition, in some of the animals which lived longer than two weeks, small tuberculous foci were noted in the lungs.

The animals infected subcutaneously with 1,000,000 bacilli were found to have extensive tuberculous involvement of the spleen, liver, lungs, site of inoculation, and the axillary lymph nodes.

Histopathologic examination: Seven segments of the spinal cord, i.e., 2 lumbar, 3 thoracic, and 3 cervical, and 3 portions of the brain, i. e., frontal, middle of the cerebrum, and cerebellum, were studied. A disseminated meningitis involving the

inner layers but not the dura mater was seen at various levels of the spinal cord (figure 3). With few exceptions, the leptomeninges of the entire cord and most of the brain were involved. The reaction was markedly cellular and consisted of histiocytes as shown in figure 4 with some lymphocytes and polymorphonuclear leukocytes. Areas of necrosis or giant cells were rarely seen. Sections stained with hematoxylin-carbol-fuchsin revealed acid-fast bacilli occurring singly or in clumps.

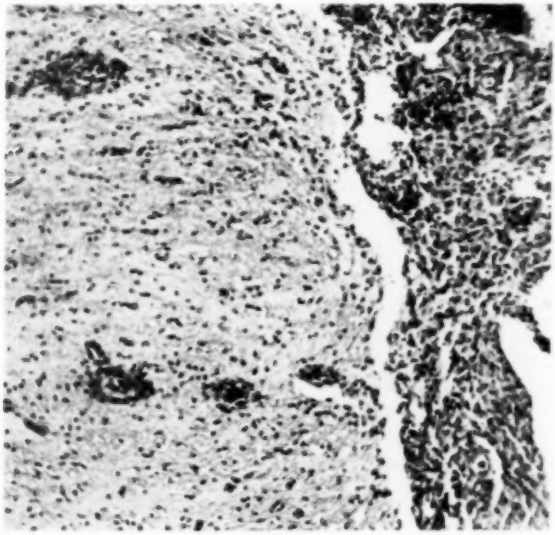

FIG. 5. Portion of cerebrum of an animal which died thirty-one days after intrathecal inoculation with 10,000 tubercle bacilli. In addition to the cellular exudate involving the meninges, four vessels may be seen in the cerebral cortex with perivascular accumulations of histiocytes. Hematoxylin-carbol-fuchsin stain revealed acid-fast bacilli seen among the cells surrounding these vessels. (Hematoxylin and eosin stain. × 100.)

In all animals except one, the entire cord was involved. One animal which survived 16 days had lesions limited to the lumbar portion of the cord. The cerebellum and the middle part of the cerebrum of each animal were the sites of extensive meningeal involvement. In the latter, the reaction was particularly severe at the base. Of the frontal lobes, two-thirds had the typical cellular reaction while the remaining third was free of meningeal involvement. There appeared to be no difference between the three groups with respect to the extent and character of the lesions.

Of particular interest was the constant occurrence of perivascular accumulations of cells in the brain and spinal cord as shown in figure 5. These were small and apparently consisted largely of histiocytes. With appropriate stains, acid-

fast bacilli could be seen in these perivascular lesions. Involvement of vessel walls also often occurred. Larger areas of tuberculous encephalitis and myelitis than are shown in figure 5 were seen in many animals. This involvement appeared to have arisen from perivascular lesions. Rarely, there appeared to be direct extension of the morbid process from the meninges into the adjacent nervous tissue.

Microscopically, the liver, lungs, and spleen of the animals infected intrathecally revealed multiple small tuberculous foci. Similar lesions were also present in lungs, which at necropsy appeared to be normal. In general, the lesions of the visceral organs were greater in extent in those animals which survived the longest. They were present in all animals, however.

The brains and spinal cords of the animals which were infected subcutaneously had no microscopic evidence of meningitis, and there was no perivascular infiltration of the cerebral vessels. The lungs, liver, and spleen of each animal in this group had widespread conglomerate tuberculous lesions with necrosis.

COMMENT

When preliminary exploratory studies were being made, it was found that lumbar puncture in guinea pigs did not yield cerebrospinal fluid in any appreciable amount. It became necessary, therefore, to devise a test for determining when the point of the needle was in the proper position in the vertebral canal. It was found that in some animals the injection of air in amounts greater than 0.1 ml. caused an immediate reaction consisting of tetany and dyspnea, accompanied by paralysis of both hind limbs. Death occurred either within a few minutes or a few days. The rapid injection of 0.02 ml. of air, however, caused only an immediate and transitory twitch of the hind limbs but no paralysis and no deaths. It was believed that in animals which did not respond in this fashion the needle was not in the vertebral canal. This proved to be the case. The injection of 0.1 ml. of methylene blue solution or of india ink following a typical reaction to the injection of 0.02 ml. of air resulted in distribution of the colored material over the surface of the brain in animals killed thirty seconds after injection. In contrast, in animals which did not respond to the injection of air, the methylene blue or the india ink was found in the paravertebral tissues but not in the brain or cord.

In a number of experiments performed subsequent to those described in the present report, a total of 294 guinea pigs have been infected intrathecally by injection of air as a test, followed by the injection of 0.1 ml. of suspension of tubercle bacilli. Four of 144 animals given 0.05 ml. of air and 2 of 150 given 0.02 ml. of air died within the first five days. These animals became paralyzed immediately after injection of the air.

SUMMARY

Intrathecal inoculation of guinea pigs may be accomplished by placing a hypodermic needle into the space between the fifth and sixth lumbar vertebrae. The needle is inserted at an angle of 45 degrees with the sacrum to a depth of 10 to 15 mm. until a bony resistance is felt. A slight jerking movement of the hind

limbs upon injection of 0.02 ml. of air indicates that the needle is in the proper position. A satisfactory reproducible tuberculous meningitis is caused regularly by the injection of 0.1 ml. of a suspension of tubercle bacilli.

The average survival time for guinea pigs inoculated with 1,000,000, 100,000, or 10,000 tubercle bacilli was 11.3, 17.4, and 24.3 days, respectively. Histologically, there was extensive exudative tuberculous meningitis involving the brain and the cord and, in addition, tuberculous encephalitis and myelitis occurred frequently. These latter changes appear to be of perivascular origin. There was also involvement of lungs, liver, and spleen. The procedure provides a means of producing tuberculous meningitis in guinea pigs for studies on pathogenesis and chemotherapy of the disease.

SUMARIO

Método para Producir Meningitis Tuberculosa en los Cobayos por Inoculación Intratecolumbar

La inoculación intratecal del cobayo puede llevarse a cabo introduciendo una aguja hipodérmica en el espacio entre la quinta y la sexta vértebras lumbares. La aguja se hunde a un ángulo de 45° con el sacro hasta una profundidad de 10 a 15 mm., hasta percibir resistencia ósea. Una ligera sacudida de los miembros traseros al inyectar 0.02 ml. de aire indica que la aguja se encuentra en la posición debida. Con la inyección de 0.1 ml. de una suspensión de bacilos tuberculosos, se produce con regularidad una meningitis tuberculosa satisfactoria y reproducible.

El tiempo medio de sobrevivencia para los cobayos inoculados con 1,000,000, 100,000 o 10,000 bacilos tuberculosos fué de 11.3, 17.4 y 24.3 días respectivamente. Histológicamente había extensa meningitis tuberculosa exudativa que invadía el cerebro y la médula, observándose además frecuentemente encefalitis y mielitis tuberculosas. Estas últimas alteraciones parecían reconocer origen perivascular. También estaban afectados los pulmones, el hígado y el bazo. El procedimiento suministra un medio de producir meningitis tuberculosa en los cobayos para estudios relativos a la patogenia y la quimioterapia de la enfermedad.

RESUME

Une méthode pour produire la méningite tuberculeuse chez le cobaye par inoculation intra-rachidienne lombaire

L'inoculation intra-rachidienne du cobaye peut être pratiquée en introduisant une aiguille hypodermique entre la cinquième et la sixième vertèbre lombaire. L'aiguille est insérée à un angle de 45° avec le sacrum, à 10 à 15 mm. de profondeur jusqu'à ce qu'une résistance osseuse soit perçue. Un léger mouvement réflexe des membres postérieurs quand 0,02 ml. d'air ont été injectés indique que l'aiguille est en place. L'injection de 0,1 ml. d'une suspension de bacilles tuberculeux permet de reproduire régulièrement l'apparition de la méningite tuberculeuse.

Le temps moyen de survie, pour les cobayes inoculés avec 1.000.000, 100.000 ou 10.000 bacilles tuberculeux, était respectivement de 11,3,17,4 et 24,3 jours. Histologiquement, il existait une méningite tuberculeuse exudative étendue intéressant le cerveau et la moelle épinière, de plus, l'encéphalite tuberculeuse et la myélite se sont fréquemment produites. Ces dernières manifestations paraissaient avoir une origine périvasculaire. Les poumons, le foie et la rate étaient également atteints. Cette méthode constitue un moyen de produire la méningite tuberculeuse chez le cobaye pour les études de pathogénèse et de chimiothérapie dans cette affection.

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TUBERCULOUS CHEST WALL SINUSES[1]

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(Received for publication June 4, 1952)

INTRODUCTION

It is well recognized that the majority of tuberculous chest wall sinuses arising *de novo*, that is, without the presence of a frank tuberculous empyema, have their origin in breaking down tuberculous parasternal lymph nodes in the anterior mediastinum. These nodes form a chain 5 to 10 in number on each side along the internal mammary vessels. They are external to the pleura, endothoracic fascia, and transversus thoracis, and lie beneath the internal intercostal muscles and in close proximity to the costal cartilages. In addition, intercostal lymph nodes are situated along the course of the intercostal arteries, either where their lateral perforating branches are given off or, more commonly, at the posterior ends of the intercostal spaces. These nodes are usually immediately outside the parietal pleura. There are also anterior, middle, and posterior diaphragmatic nodes.

The drainage of the hilar lymph nodes is almost entirely upwards along the trachea, so it is an interesting question how these parietal lymph nodes of the chest wall become infected. Burke (1) has shown that when particulate matter (lamp black, colloidal thorium dioxide, and tubercle bacilli) is introduced into the pleural space of guinea pigs, it is, in part at least, regularly conveyed to the parasternal nodes. In a group of fourteen cases of spontaneous cold abscesses of the chest wall reported by him, ten at least have a clear history of antecedent or coexistent pleurisy. The course of events appears to be that tubercle bacilli invade the pleura, and a local or widespread pleuritis results. Some bacilli are transported to the parasternal lymph nodes, and months or years later these nodes may break down and the pus burrow externally between the ribs or costal cartilages. Necrotic cartilage is nearly always present, and the remains of caseous nodes can often be demonstrated at operation.

These essential points of pathology give the clue to the correct surgical treatment. The remains of the caseating lymph nodes must be thoroughly removed. In addition, all tuberculous granulation tissue, involved portions of ribs, and, in particular, diseased cartilage must also be excised. As Maier (2) points out, hyaline cartilage is not supplied by any blood vessels and derives its nutrition from the lymph. It is thus very vulnerable to infection and, if left exposed, may become necrotic and act as a foreign body. Consequently, the treatment of chondritis is resection and, if any part of the seventh to tenth costal cartilages is diseased, then ideally the whole costal arch on that side should be resected. This was emphasized as long ago as 1918 by Moschowitz (3). The present writers believe, however, that nowadays with antimicrobial therapy such a radical procedure is not necessarily required if healthy cartilage exposed in the wound can be covered

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with muscle or a sheath of perichondrium and the wound be closed. Obliteration of dead space is an essential point in all surgery of tuberculous tissues. It is doubtful if tubercle bacilli can infect healthy tissue in a wound in the absence of a dead space containing culture media like blood or serum.

The following cases, 5 before the days of streptomycin and 6 in which the drug was used, illustrate the writers' surgical experience over the past ten years. These are the cases in which radical surgery was attempted. There are also cases, probably with little involvement of rib or costal cartilage, in which prolonged bed rest alone or adequate drainage and streptomycin therapy will in time effect a sound healing. One such case was that of a European immigrant who, in addition to his streptomycin, insisted on applying onion and garlic poultices to his sinus which poultices he subsequently ate. This mild eccentricity was not to be construed as a sign of psychopathology, however, but rather of strength of character, in that while tolerating modern ideas he also stuck to the well-tried methods of his forebears. His sinus has remained well healed.

OBSERVATIONS

Pre-Streptomycin Cases

Case 1. F. F., a Hebrew female, was twenty-four years old when admitted to this hospital on January 3, 1941. The previous July she had developed pain in the right upper quadrant of the abdomen; and, in September, 1940, a laparotomy had revealed a tuberculous abscess arising from the region of the ninth costal cartilage. A chronic sinus resulted. There was no evidence of tuberculosis in the lungs or elsewhere; and there was no history of pleurisy, although it was difficult to be sure of this as she spoke no English. On July 7, 1941, the scar of the former operation was excised and the sinus was followed up to the right eighth and ninth costal cartilages through the lower fibers of the *pectoralis major*. A quantity of tuberculous granulation tissue surrounded these cartilages, which were removed, and all tuberculous granulation tissue beneath them was also excised. The wound was packed with iodoform gauze. She was discharged on December 11, 1941, with the sinus almost healed. Final healing did not occur, however, for more than eight years. When last seen in November, 1951, the sinus had been healed for twenty months.

Comment: Excision was clearly not sufficiently radical in this case, and it will be noted that there was no attempt to obliterate the dead space or close the wound.

Case 2. H. P., a white male, was twenty-nine years old on admission to this hospital on June 22, 1938. Far advanced pulmonary tuberculosis was present which involved the whole of the left lung and the upper third of the right lung. An artificial pneumothorax had been present on the left for two years, but an effusion had developed and the fluid was positive for tubercle bacilli on culture. The patient was given gold therapy and in 1938 to 1939 a left-sided, 11-rib thoracoplasty was performed in four stages. He made good progress until June 1941, when a cold abscess appeared in the region of the seventh left costal cartilage followed by the development of a sinus. In April, 1942, the sinus tract was excised. It was found to extend further than was expected, but excision of one inch of the seventh costal cartilage seemed to expose it fully. The wound was washed out with tincture of iodine and closed. Primary healing occurred, but in July, 1942, a fresh abscess appeared above the scar. In September, 1942, a fresh incision was made along the left fifth rib and costal cartilage. An abscess cavity was dissected out, including three inches of the fifth rib and a portion of its cartilage. The wound was closed, and again it healed. In January, 1943, an abscess ap-

peared under the scar of the first operation; and, in March, 1943, a third attempt was made to eradicate the disease. The tract was found extending under the seventh rib and what remained of its cartilage, and further excision was done and the wound closed and again it healed. Nevertheless, rapid extension of the pulmonary disease followed, and the patient died on December 21, 1943.

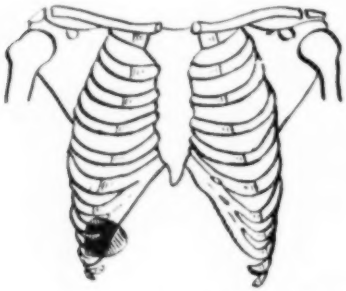

FIG. 1. *Case 1.* (F. F.) Diagram showing extent of excision.

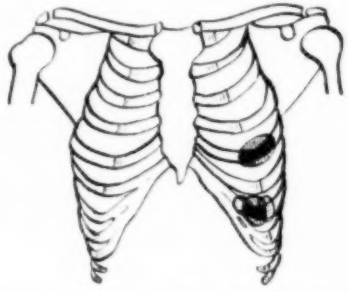

FIG. 2. *Case 2.* (H. P.) Diagram showing extent of excision in three operations.

FIG. 3. *Case 3.* (E. B.) Roentgenogram showing cold abscess behind sternum.

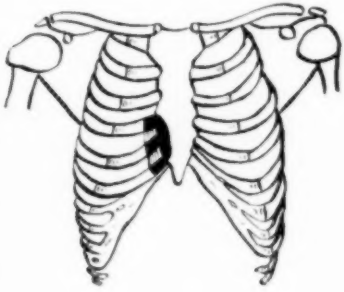

FIG. 4. *Case 3.* (E. B.) Diagram showing extent of excision.

Comment: In the light of present experience the first operation should have been more radical and an attempt should have been made to close the wound without using an irritant like tincture of iodine. However, the inability of the patient to control his tuberculosis may have contributed to the recurrences of the abscess.

Case 3. E. B., a white female, was thirty-four years old on admission to the hospital on October 17, 1944. In February, 1937, she had a left pleurisy with effusion which was treated by rest and aspiration. She remained well until February, 1940, when a small painless lump appeared over the sternum. This was diagnosed as a sebaceous cyst, was excised and healed, but a few months later returned. The lesion gradually increased in size and finally in July, 1944, ruptured and discharged pus. It was investigated at another hospital and on October 1, 1944, was explored and a large substernal tuberculous abscess was found. Part of the right margin of the sternum and involved costal cartilages were removed and the wound was sutured. Healing by first intention followed, and the patient was transferred to this hospital for after-care. The wound remained healed although roentgenograms showed an abscess still present behind the sternum. The patient was discharged on March 17, 1945, and has been followed regularly as an outpatient. The retrosternal abscess slowly enlarged over the next four years, but since then has been stationary and there has recently been recalcification of the sternum. There has been no recurrence of the sinus, and she is otherwise in good health.

Comment: The excision was not radical enough to prevent a recurrence of the retrosternal abscess, but the patient's own resistance has been sufficient to keep the tuberculosis under control.

Case 4. E. R., a white female, was seventeen years old on admission to the hospital on April 15, 1944. The diagnosis on admission was *pulmonary tuberculosis, bilateral, minimal, active, B. bacillary*, with a small pleural effusion on the right. Artificial pneumothorax was attempted on both sides but had to be abandoned. In February, 1946, it was decided to perform a left six-rib thoracoplasty but, while waiting for this operation, she developed a cold abscess in the lower part of the right breast. The left thoracoplasty was carried out in March, 1946; and on April 29, 1946, the cold abscess was explored. A curved incision was made under the fold of the right breast. The fourth and fifth ribs were found to be bare and eroded and surrounded by tuberculous granulation tissue. Segments of these ribs were excised, together with all diseased tissue down to the parietal pleura. Cartilage was not exposed. In addition, a segment of breast was excised. The dead space was obliterated and the wound closed. Microscopic examination of the excised tissue revealed the presence of tuberculous infection. There was some oozing after the operation, but the wound finally healed after approximately two months and has remained healed ever since.

Comment: Radical excision and obliteration of the dead space has resulted in permanent healing of the tuberculous abscess.

Case 5. M. D., a white female, was twenty-one years old on admission to the hospital on May 27, 1944. Active tuberculosis of the left sacroiliac joint was present, and a tuberculous abscess in the right breast had been excised before admission but had left a discharging sinus. This abscess was not primarily in the breast but originated in the parasternal nodes and also involved the right fourth and fifth costal cartilages. There was no history of pleurisy, and the lungs were normal. Her bone and joint disease proved difficult to manage. She had an extra-articular arthrodesis of the left sacroiliac joint, but it broke down and was treated by saucerization and sequestrectomy, with final healing. Pott's disease of the fifth lumbar vertebra was treated by spinal fusion. The patient developed renal calculi due to recumbency and showed evidence of amyloid disease.

On June 20, 1946, the chest wall sinus was explored. Two inches of each of the right fourth and fifth costal cartilages were excised and all diseased tissue was curetted away. One tract seemed to run right through the fifth costal cartilage and terminate in the perichondrium on its deep aspect. No evidence of caseous lymph nodes was found. The wound was washed out with a liter of normal saline and closed. Eight months were required for the wound to heal completely, but when last examined in August, 1949, it had remained healed.

Comment: The operation apparently did not remove all of the tuberculosis of the soft tissues as the wound took so long to heal. If streptomycin had been available at that time, healing might have been more prompt, although that is no excuse for inadequate surgery.

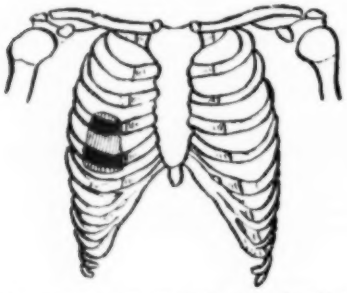

FIG. 5. *Case 4.* (E. R.) Diagram showing extent of excision.

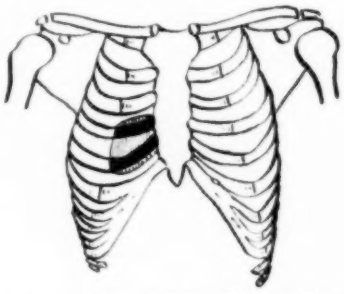

FIG. 6. *Case 5* (M. D.) Diagram showing extent of excision.

Cases in Which Streptomycin Was Used

Case 6. H. L., a Chinese male, was thirty-two years old on readmission to the hospital on February 25, 1948. In 1941, a tuberculous abscess had appeared over the lower part of the right anterior chest wall. This was incised and drained, and in July, 1943, radical excision was attempted. An incision was made over the right seventh costal cartilage, and this cartilage and part of the seventh rib were excised, together with a mass of caseous material and tuberculous granulation tissue. It was found impossible to obliterate the space left, but the incision was closed. Quiescent tuberculous abscesses were also present in the anterior mediastinum deep to the right third, fourth, and fifth ribs but without sinuses, and these were not touched. A right phrenicolasia was done, but a right thoracoplasty was postponed because of his chest wall infection. The sinus over the anterior end of the right seventh rib did not heal, but he was discharged in 1944. He was readmitted in February, 1948, and a right six-rib thoracoplasty was performed. Cultures from the sinus over the seventh rib still yielded tubercle bacilli, and roentgenograms showed evidence of erosion of the anterior end of the right third rib with a subpectoral abscess. On September 14, 1949, an incision was made over the anterior end of the right seventh rib. Approximately one inch of this rib was removed as well as the remains of the seventh costal cartilage and parts of the sixth and eighth costal cartilages, and the abscess cavity which measured two and one-half by three inches was unroofed. A flap of *rectus abdominis* was sutured into the cavity to obliterate it, and the wound was closed. The operation was accompanied and followed by a thirty-day course of 1.0 gm. of streptomycin daily. The wound healed by first intention and has remained healed. The quiescent abscesses beneath the right third, fourth, and fifth ribs were not touched.

Comment: The second radical operation with obliteration of the space with a muscle transplant and streptomycin therapy resulted in immediate and complete healing.

Case 7. H. W., a white male, was twenty-four years old on admission to the hospital on February 22, 1944. He had miliary tuberculosis of the lungs, arrested, and active tuberculosis of the spine (second and third lumbar vertebrae), left sacroiliac joint, left knee, and

left hip. An arthrodesis of the left knee and hip was performed, and the spine was fused. In April, 1949, a small abscess appeared below the xiphoid process and the pus proved positive for tubercle bacilli on culture. Lipiodol injection revealed a tract running up behind the sternum and then laterally for two and one-half inches behind the left sixth rib.

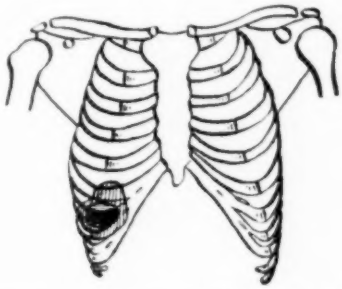

FIG. 7. *Case 6* (H. I.) Diagram showing extent of excision.

FIG. 8. *Case 7*. (H. W.) Injection of lipiodol showing tract running up behind sternum and along left sixth rib in front.

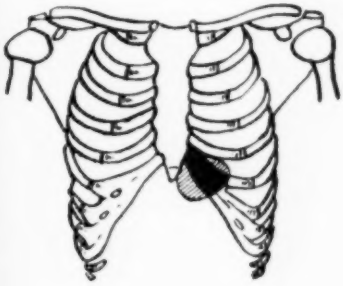

FIG. 9. *Case 7*. (H. W.) Diagram showing extent of excision.

On October 5, 1949, radical excision was done. The left costal margin, including parts of the sixth and seventh cartilages, was excised together with the whole sinus wall which included a section of pericardium. In doing this, a small tear was made in the left pleura and this was oversewn. Part of the left *rectus abdominis* was sutured over the exposed edges of cartilage and to the pericardium and the diaphragm, which was exposed below, and the wound was closed. Healing occurred by first intention, and there has been no recurrence. The operation

was "covered" by a thirty-day course of streptomycin administered twice daily in 0.5 gm. doses.

Comment: The bare ends of healthy cartilage were covered by muscle, and no necrosis followed. A "radical" excision means removing all tuberculous tissue including pericardium.

Case 8. W. C., a white male, was twenty-one years old on admission to the hospital on October 29, 1946. He had Pott's disease of the vertebrae from the eleventh dorsal to the first lumbar which was treated by spinal fusion. There was no evidence of pulmonary disease or history of pleurisy. In November, 1945, a lump had appeared over the left sixth chondrosternal junction, and pus from it yielded tubercle bacilli on culture. In addition, a sinus appeared over the right third costal cartilage. Streptomycin, 0.5 gm., was injected into these sinuses periodically and in August and September, 1948, a sixty-day course of streptomycin, 0.5 gm. twice daily by the intramuscular route, was given with some improvement but not actual healing. The sinuses were too small for lipiodol injection. On January 11, 1950, an incision was made over the lower of the two sinuses. The left fourth, fifth, and sixth costal cartilages were removed together with all tuberculous granulation tissue. This involved ligating the left internal mammary vessels and exposing the diaphragm below. The left pleura was torn and oversewn and the lung was reinflated. There did not appear to be any communication behind the sternum with the sinus over the right third costal cartilage. There was no muscle available for filling the defect, and the wound was closed as well as could be managed. The operation was "covered" by a course of streptomycin, 1.0 gm. daily for thirty days, with penicillin, 200,000 units daily for nineteen days. The small sinus over the right third costal cartilage continued to discharge, and on March 1, 1950, this costal cartilage and a piece of the third rib were removed together with all the granulation tissue. The wound was closed. Penicillin was given with this second operation but no streptomycin was administered. Both wounds healed by first intention and when last seen in November, 1950, the patient was in good health.

Comment: Radical excision must be done even if it includes damage to, or excision of, the parietal pleura. The use of streptomycin and, if necessary, penicillin makes the procedure safe so long as no dead space is left.

Case 9. H. O., a white male, was fifty years old on admission to the hospital on June 26, 1950, with minimal pulmonary tuberculosis. A cold abscess had appeared over the left sternoclavicular joint and another over the lower end of the sternum in September, 1949. The lower one had burst in December, 1949, and the upper one had been incised during streptomycin therapy in February, 1950. Tubercle bacilli were cultured from both sinuses. Lipiodol injection was unsatisfactory, but the upper sinus appeared to burrow down behind the sternum for some distance. On July 19, 1950, the sinus over the left sternoclavicular joint was explored. Tuberculous arthritis of the joint was present, and it was found necessary to remove the inner end of the clavicle, the sternoclavicular joint, the major part of the manubrium, and the right first rib cartilage. All the granulations were curetted, and one pocket still deeper under the manubrium was cauterized with pure carbolic acid and alcohol. The wound was then closed. The operation was "covered" by a twenty-three day course of 1.0 gm. of streptomycin daily with 2.0 gm. of *p*-aminosalicylic acid (PAS) daily. The small dose of PAS was part of a research program being carried out at that time. On September 27, 1950, the lower sinus was explored. The cartilages of the right fourth, fifth, and sixth ribs were removed with part of the sternum and a section of parietal pleura. The right internal mammary vessels were ligated. The gap in the pleura was closed by suturing down the *pectoralis major*, and the wound was closed. The operation was "covered" by a thirty-day course of streptomycin, 1.0 gm., and PAS, 2.0 gm., daily. The wounds both healed by first

intention and so far have remained healed. There was very little limitation of movement of the left arm following the loss of the sternoclavicular joint.

Comment: Loss of the left sternoclavicular joint and of a section of parietal pleura was necessary to eradicate the tuberculous disease in this patient.

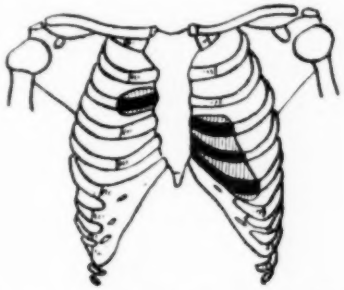

FIG. 10. *Case 8.* (W. C.) Diagram showing extent of excision in two operations.

FIG. 11. *Case 9.* (H. O.) Roentgenogram showing resection of left sternoclavicular joint.

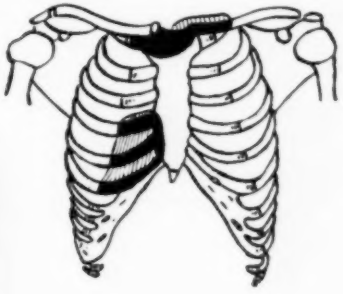

FIG. 12. *Case 9.* (H. O.) Diagram showing extent of excision in two operations.

Case 10. E. E., an eight-year-old Eskimo boy, was admitted to the hospital on March 17, 1951. For an unknown number of years, probably since early childhood, he had had a discharging sinus on the right anterior chest wall just below and lateral to the nipple. The lung fields were clear but there was evidence of an old pleurisy on the right side. The right fifth and sixth ribs were markedly irregular in the roentgenogram and gave the appearance of reformed ribs following resection, but actually the abnormalities represented interference with growth due to the long-standing infection. Cultures were positive for tubercle

bacilli and for a hemolytic *Staphylococcus aureus*. Injection of lipiodol showed two sinus tracts extending backwards for perhaps five inches along these two ribs. A course of penicillin and Gantrisin was given to help clear up the secondary infection, and on October 3, 1951, radical excision was done. A curved incision was made along the line of the right fifth rib, and the fifth and sixth ribs were removed from the tips of the transverse processes behind, almost to the cartilages in front. The disease did not extend completely to the cartilages, however, and care was taken not to expose them. The rib beds, including the periosteum, were excised entirely, leaving only thickened parietal pleura except in the region of the opening of the sinus in front, where it was also necessary to remove an area of pleura. The pleural space was obliterated, however, and, although there was some retraction of the

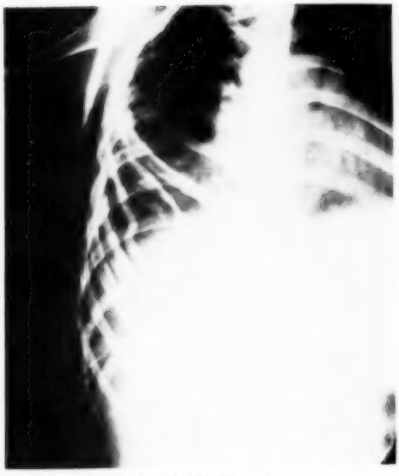

FIG. 13. *Case 10.* (E. E.) Roentgenogram showing deformity of right fifth and sixth ribs.

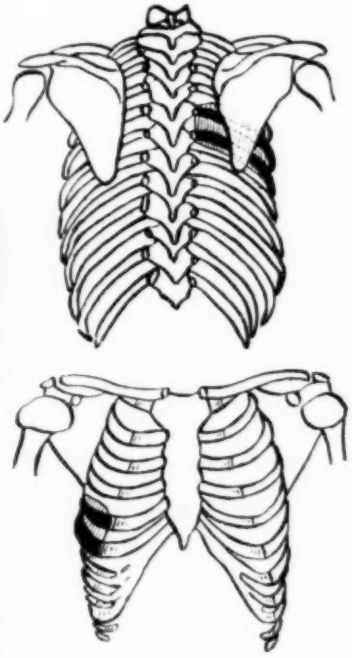

FIG. 14. *Case 10.* (E. E.) Diagram showing extent of excision.

underlying lung, no pneumothorax developed. Blood vessels in the rib beds appeared arteriosclerotic and in some places failed to retract. The posterior end of the incison was closed by approximating the fourth and seventh ribs, but this was not possible in front and the gap was closed by suturing down the *serratus anterior*. The operation was "covered" by a fifteen-week course of streptomycin, 1.0 gm. twice weekly, with PAS, 10.0 gm. daily. In addition, the patient received penicillin and later aureomycin for a hemolytic staphylococcal infection of the wound, but good healing occurred with a sound scar and he is now ready to return north to James Bay.

Comment: The whole of the two ribs with their periosteum had to be removed to eradicate the disease, and the closure of the gap may result in some degree of

scoliosis although there is no sign of that at present. The possibility of scoliosis was a calculated risk which had to be taken. The source of the infection was probably liquefying intercostal nodes rather than parasternal lymph nodes.

Case 11. J. S., a white female, was twenty-nine years old on admission to the hospital on November 17, 1951. There was a discharging sinus in the fold under the right breast. A cold abscess had first appeared in 1948, and there had been three previous unsuccessful attempts at excision before admission to this hospital. The lungs were normal, and there was no history of pleurisy although at operation pleural symphysis was present. Injection of lipiodol showed small tracts running deep to the right sixth and seventh costochondral junctions. Cultures from the sinus were positive for tubercle bacilli and also yielded a hemolytic *Staphylococcus aureus*. She was started on a course of Gantrisin, and on October 31, 1951, the sinus was explored. Both the sixth and seventh right costal cartilages were bare and eroded. One inch of the sixth rib and an inch of its cartilage were removed together with most of the seventh cartilage. The parietal pleura was adherent to the deep surface of the perichondrium and was cut away, but the pleural space beneath was found to be obliterated and

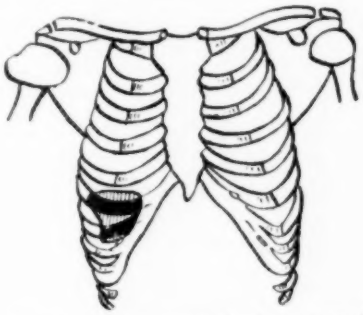

FIG. 15. *Case 11.* (J. S.) Diagram showing extent of excision.

no pneumothorax resulted. The wound was closed, apart from a small drainage tube for twenty-four hours. The wound healed soundly by first intention. The operation was covered by a three-month course of streptomycin, 1.0 gm. twice weekly, with PAS, 10.0 gm. daily.

Comment: Although the time interval is short, there is every reason to expect that sound healing has occurred.

The following case, although not strictly one of a tuberculous chest wall sinus, is included on account of its unusual nature.

Case 12. G. M., a white male, was fifty-four years old on admission to the hospital on March 8, 1937. The diagnosis on admission was pulmonary tuberculosis, minimal, nonbacillary, Pott's disease of the ninth dorsal vertebra with paravertebral abscess, and spondylolisthesis. Shortly after admission, evidence of miliary tuberculosis appeared and the patient died on January 1, 1938. At autopsy, he was found to have multiple tuberculous abscesses in the ribs with eighteen pathologic fractures in fourteen ribs.

DISCUSSION

It is believed that the experience in these 11 cases of tuberculous chest wall sinuses treated by radical excision confirms the generally accepted view that the majority of these sinuses have their origin in liquefying lymph nodes, usually the

parasternal nodes. It is easy to understand how these nodes become infected through the lymphatic channels from the pleura. Once they have broken down, the sinuses may discharge for years unless the remains of the nodes and all diseased tissue are thoroughly excised.

Virtually all such cases are secondarily infected by the time of operation, and an attempt should be made to eliminate the nontuberculous infection if possible. Injection of lipiodol will often help in outlining the direction and extent of the sinuses. The present practice of the writers is to accompany and follow the operation by a three-month course of streptomycin in 1.0 gm. doses twice weekly with 10.0 gm. of PAS each day.

Perhaps even more important than the streptomycin, however, are two points in the surgical technique:

(*1*) The operation should be radical. This is never a minor operation. Intratracheal anesthesia should be given as it may be necessary to excise part of the pleura and open the chest. A blood transfusion should be running during the procedure because blood loss is often heavy. Sinuses must be followed to their limit and all diseased tissue removed — sternum, ribs, cartilage, caseating lymph nodes, and even pleura and pericardium. In one of the present cases, the inner end of the clavicle and the sternoclavicular joint had to be sacrificed.

(*2*) Dead space must be obliterated and the wound closed. It is doubtful if tubercle bacilli can infect healthy tissue in a wound in the absence of a dead space containing blood or serum acting as a culture medium for their propagation. Following this principle, it has not been found necessary to excise all *exposed* cartilage so long as the diseased portion is thoroughly removed and bare ends can be covered with perichondrium or a muscle flap.

All 6 of the second group of patients treated in this manner and assisted by streptomycin "coverage" have healed well and the abscesses have not recurred, although the follow-up in the most recent cases is too short to be conclusive on this point.

SUMMARY

Eleven cases of tuberculous chest wall sinuses treated by radical excision are presented. Chest wall sinuses usually arise from liquefying lymph nodes which were infected from the pleura. The operation is accompanied and followed by a course of streptomycin and *p*-aminosalicylic acid. Excision should be extensive and all tuberculous tissue removed. In addition, the dead space should be obliterated and the wound closed. With such radical treatment, these sinuses should heal well and cause no further trouble.

SUMARIO

Fistulas Tuberculosas de la Pared Torácica

Preséntanse 11 casos de fístulas tuberculosas de la pared torácica tratadas con la excisión radical. Las fístulas de la pared torácica suelen ser creadas por la desintegración de ganglios linfáticos infectados de la pleura. La operación va acompañada de una tanda de estreptomicina y de ácido *p*-aminosalicílico. La excisión debe ser extensa y debe eliminar todo el

tejido tuberculoso. Además, hay que obliterar todo espacio desvitalizado y que cerrar la herida. Atacadas radicalmente de esa manera, dichas fístulas deben cicatrizar bien, sin ocasionar más perturbaciones.

RESUME

Fistules tuberculeuses de la paroi thoracique

Présentation de onze cas de fistules tuberculeuses pariétales traitées par excision radicale. Les fistules de la paroi thoracique sont formées par la destruction de ganglions lymphatiques infectés par la plévre. On administre aux malades de la streptomycine et de l'acide *p*-aminosalicylique pendant et après l'operation. L'exerèse doit être extensive, tous les tissus tuberculeux doivent être excisés. De plus, l'espace vide doit être comblé et la plaie refermee. Traitées radicalement, ces fistules devraient guérir complétement et sans séquelles.

Acknowledgments

The operations was carried out under the supervision of Professor R. Janes and Dr. F. G. Kergin, consultants in thoracic surgery, Toronto Hospital for Tuberculosis, Weston, Ontario.

The writers wish to express their indebtedness to Dr. C. A. Wicks, Superintendent, and Dr. H. S. Coulthard, Chief of the Surgical Service; also to Mr. R. H. Giffin and the radiological staff for the photographs.

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PARTIAL NEPHRECTOMY FOR TUBERCULOSIS[1,2]

JOHN K. LATTIMER

(Received for publication March 24, 1952)

INTRODUCTION

When tuberculosis involves only part of a kidney, the urologist can now remove that segment of the kidney just as the modern chest surgeon removes tuberculous portions of the lung. Streptomycin, para-aminosalicylic acid (PAS), and new surgical techniques have sharply reduced the incidence of fistula formation and fatal miliary dissemination which accompanied this operation in the past.

It has been the experience of the Veterans Administration Research Unit for Genito-Urinary Tuberculosis that surgical excision is the most satisfactory treatment for fibrocaseous, necrotic renal lesions. Such lesions can rarely be sterilized by chemotherapy alone, although medical treatment may indeed slow the progress of the lesion. At this Center, partial nephrectomy for tuberculosis has therefore become a standard procedure, applicable to the few patients with renal tuberculosis who meet certain criteria. Dr. Carl Semb, of Oslo, Norway, (1) has done much to encourage the use of partial nephrectomy in the Scandinavian countries and in France. Semb has demonstrated that it is possible to resect a middle calyx as successfully as an end calyx. Both Semb's patients and those of the present writer, however, showed a much greater tendency towards involvement of the upper calyx. Semb has resected the upper pole of the kidney in 45 instances, the middle portion in 8, the lower in 16, and the upper and lower poles in 3 (2).

CASE SELECTION

Less than 5 per cent of the cases of renal tuberculosis observed by the present writer have been suitable for partial nephrectomy. Since renal tuberculosis appears to be an infection by multiple simultaneous blood-borne bacilli, it has been unusual to detect the disease in a stage when only one of these foci has begun to break down, so that activity is confined to only one segment of the kidney. In order that the operation may succeed, it is essential that the disease has not yet spread to other portions of the renal pelvis. It is also necessary that the anatomic characteristics and the vascular supply of the kidney be such as to permit resection of the entire lesion plus a margin of uninfected kidney tissue. Moreover, it is desirable to know that the activity of the lesion has been reduced to an op-

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[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

timum point by chemotherapy, rest, and the healing process. It is further advisable that any pulmonary, osseous, or lymphatic tuberculous foci elsewhere in the body be completely quiescent before operation on the kidney is contemplated.

At the Veterans Administration Research Unit, only 5 of the patients fulfilled all of these criteria during the year of 1951. The present report is concerned with the operative procedure used in these patients and the results thereby obtained. The renal lesions of all of the patients have remained negative for *M. tuberculosis* by urine culture since operation, but the longest postoperative interval has been only eighteen months. The other patients have been observed postoperatively for seventeen, sixteen, eight, and six months, respectively, as of November 1, 1952.

PREOPERATIVE PREPARATION

Multiple (three) retrograde pyelogram films were taken on at least two occasions in an effort to rule out involvement of additional segments of the kidney. The patients were given a minimum of 120 days of chemotherapy preoperatively, which usually consisted of 1 gm. of streptomycin and 12 gm. of PAS each day.

A renal arteriogram was obtained in those cases in which a preoperative study of the branches of the renal artery was deemed desirable. One patient was spared an operation by this maneuver when the arteriogram revealed that the renal artery entered the diseased half of a double kidney before turning to supply the normal half. This would have made partial nephrectomy impossible.

TECHNIQUE OF OPERATION

A large incision was always employed to permit adequate control of the renal artery during the incision of the kidney. For high kidneys, a rib was usually resected or a Nagamatsu type of incision was employed. Great care was taken to avoid manipulation of the tuberculous portion of the kidney in order to minimize the dislodging of tubercle bacilli into the blood stream during partial nephrectomy. The renal vessels were cleared of surrounding fat and fascia to permit the application of a soft, rubber-shod intestinal clamp when necessary. The aberrant vessels which were frequently found leading into tuberculous areas (possibly the route of infection) were ligated and cut. The kidney capsule was then excised liberally over the entire area of tuberculous involvement which had been indicated by the pyelogram or by the presence of adherent fat. The capsule was then peeled back well beyond the suspected areas. Indentations on the kidney surface revealed the presence of tuberculous areas beneath. The true extent of these areas became obvious only after the capsule was stripped back. Occasionally, bulging caseous abscesses of the parenchyma or pedunculated cystic masses also became visible.

The soft, rubber-shod intestinal clamp was then applied to the renal vessels, or the vessels were occluded with the fingers or tourniquet. The parenchyma of the kidney was incised, preferably with the blunt edge of the knife handle, approximately 1 cm. proximal to the tuberculous areas. The blunt dissection was carried down to the arcuate arteries and to the neck of the involved calyx. These tough structures resisted the blunt dissection and could be isolated, cut, and

ligated individually. The clamp or tourniquet was released at least every twenty minutes in order to avoid prolonged ischemia and to locate additional bleeding points. "Bleeders" which had been cut or torn were easily controlled by pinpoint fulguration or by suture ligatures, which pulled a small pad of fat down over each bleeding point. Pressure with a fragment of Gelfoam checked any remaining oozing.

The flaps of capsule, minus any portions which had been adherent to tuberculous areas, were then closed over the cut end of the kidney. Pads of fat or Gelfoam, included under the capsule, were rarely necessary to control oozing.

FIG. 1. Tuberculous cavities (arrows) were confined to upper portions of this kidney. Following 120 days of streptomycin therapy, the cavities stopped enlarging, and the urine remained negative for tubercle bacilli for four years. When the ureteral culture again became positive, the upper two-thirds of the kidney were resected. Postoperatively, the urine became negative for tubercle bacilli and has remained negative for eighteen months.

The wound was flushed with streptomycin solution. As a precaution, a drain was left in the corner of the wound for three to five days to permit the early detection of any bleeding. No postoperative bleeding has occurred in any case to date despite vigorous coughing on the part of a few patients during the postanesthetic period.

A further refinement of technique was employed in cases in which the best line of excision was obvious. As soon as the extent of the tuberculous lesion had been determined, it was sometimes possible to isolate the entire tuberculous end of the kidney by applying a preliminary occlusive cobbler's stitch across the end of the

kidney at the line of contemplated amputation. This stitch included the kidney capsule and was designed to occlude the venous circulation. Thus, tubercle bacilli which were dislodged from the active lesion could not find their way into the blood stream during excision of the involved end of the kidney. This cobbler's stitch was not expected to provide hemostasis since the line of excision corresponded to the line of the stitch, thus rendering the stitch useless as soon as the incision was made. It seemed preferable to ligate large vessels individually and to control others by pinpoint fulguration or suture ligature rather than to crush the entire end of a tuberculous kidney in a mass ligature. Only rarely was a second cobbler's stitch, placed some distance proximal to the line of excision, necessary

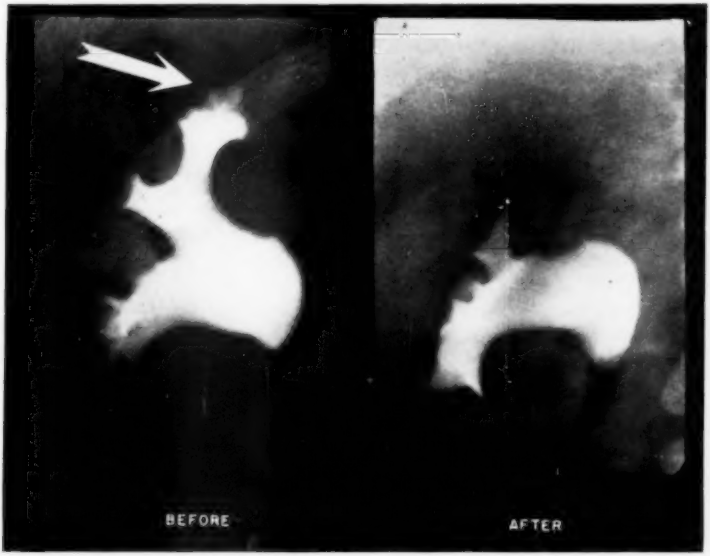

FIG. 2. The tuberculous lesion in this kidney (arrow) was limited to a cavity adjacent to the upper calyx. This portion of the kidney was amputated and the urine has since been negative for tubercle bacilli for seventeen months.

for hemostasis. Any small tuberculous areas which might be left behind in this stump of avascular tissue above the cobbler's stitch might cause widespread tuberculous necrosis.

POSTOPERATIVE CARE

In an attempt to protect against the consequences of the release of tubercle bacilli into the blood stream during operation, all patients were given 0.5 gm. of streptomycin every six hours and 20 gm. of PAS twice daily by clysis on the day of operation and for the first two postoperative days. After this, PAS was given orally at the rate of 3 gm. four times daily and streptomycin was continued for

one week. After one week, streptomycin was reduced to 1 gm. daily for two additional weeks. It was then further reduced to 1 gm. every third day and was continued as long as any pyuria was present. If the renal tuberculosis was bilateral or if prostatic tuberculosis was present, the combined chemotherapeutic regimen of streptomycin, 1 gm. every third day, and PAS, 12 gm. daily, was continued for a period of at least one year. Renal function and urine volume were reduced in these kidneys in proportion to the amount of kidney tissue removed. In all of the patients operated upon under this regimen, the urine has remained negative for tubercle bacilli for at least four months after operation. The follow-up periods are not yet long enough nor are numbers of cases large enough to be significant as yet. Semb reports that only 6 of 63 of his kidney patients subjected to partial nephrectomy for tuberculosis excreted tubercle bacilli in the urine again during the first nine months after treatment. Most of his patients also received vigorous chemotherapy before, during, and after operation.

SUMMARY

Partial nephrectomy for tuberculosis should differ from partial nephrectomy for other causes in the following particulars:

The active tuberculosis must be confined to only one segment of the kidney. It must not have spread to adjacent areas of the renal pelvis or calyces.

The vascular supply of the kidney must be located in a position which will permit resection of the diseased area.

Any pulmonary, osseous, or lymphatic tuberculous foci elsewhere in the body should be quiescent before partial nephrectomy is attempted.

Prolonged and intensive preoperative and postoperative chemotherapy should be given to reduce the activity of the tuberculous lesions.

Manipulation of the tuberculous portion of the kidney should be strictly avoided while freeing the pedicle and excising the tuberculous areas.

The renal capsule should be peeled back liberally in order to reveal the true extent of the tuberculous areas.

The renal pedicle should be occluded by a soft rubber-shod intestinal clamp or by the surgeon's fingers or a tourniquet during the actual manipulation of the kidney. This will help to prevent the dissemination of tubercle bacilli.

The wound should be flushed with streptomycin solution when the operation is completed.

The advent of streptomycin and para-aminosalicylic acid (PAS) therapy for renal tuberculosis has reduced the incidence of fistula formation and of fatal miliary dissemination to the point where partial nephrectomy for tuberculosis is now a practicable procedure. The operation is applicable, however, to only a few highly selected cases.

SUMARIO

La Nefrectomía Parcial por Tuberculosis

La nefrectomía parcial por tuberculosis discrepará de la ejecutada por otras causas en los siguientes puntos:

La tuberculosis activa tiene que estar limitada a un solo segmento renal, sin haberse esparcido a las zonas adyacentes de la pelvis o los cálices renales.

El riego vascular del riñón debe estar radicado en un sitio que permita resecar la zona patológica.

Antes de emprender la subnefrectomía, deben estar quiescentes todos los focos tuberculosos, ya sean pulmonares, óseos o linfáticos, de otras partes del cuerpo.

A fin de atenuar la actividad tuberculosa, hay que administrar prolongada e intensa quimioterapia pre- y postoperatoria.

Hay que evitar escrupulosamente toda manipulación de la porción tuberculosa del riñón mientras se congela el pedículo y se excinden las zonas tuberculosas.

Hay que denudar bien hacia atrás la cápsula renal a fin de revelar la verdadera extensión de las zonas tuberculosas.

Hay que ocluir el pedículo renal con una pinza intestinal forrada de caucho blando, con los dedos del cirujano o con un torniquete mientras se manipula el riñón. Esto ayudará a impedir la diseminación de bacilos tuberculosos.

Terminada la operación, la herida será inundada con solución de estreptomicina.

El advenimiento de la quimioterapia con estreptomicina y ácido para-aminosalicílico (PAS) en la tuberculosis renal ha rebajado la incidencia de fístulas y de granulia letal a tal punto que la nefrectomía parcial ya resulta factible. No obstante, la operación sólo es aplicable a algunos casos muy seleccionados.

RESUME

Néphrectomie partielle pour tuberculose

La néphrectomie partielle pour tuberculose doit différer de la néphrectomie pratiquée pour toute autre cause par les points suivants:

La tuberculose en activité doit être localisée à un seul segment du rein. Elle ne doit pas être étendue aux zones adjacentes du bassinet ou des calices du rein.

Le système vasculaire du rein doit être situé de telle manière que la résection du segment interessé soit possible.

Tout foyer tuberculeux pulmonaire, osseux ou lymphatique situé en un point quelconque de l'organisme devra être stabilisé avant qu'une néphrectomie partielle soit entreprise.

Il y a lieu de pratiquer une chimiothérapie intensive pré et post-opératoire prolongée pour réduire l'activité du processus tuberculeux.

Toute manipulation du segment tuberculeux du rein sera soigneusement évitée pendant la libération du pédicule et l'excision des tissus tuberculeux.

La capsule du rein devra être largement écartée pour que la véritable étendue de la zone tuberculeuse soit révélée.

L'occlusion du pédicule du rein à l'aide d'une pince intestinale à mors recouverts de caoutchouc souple ou par les doigts du chirurgien, ou encore par un ligature provisoire, devra être faite pendant la phase de manipulation du rein. Ce procédé aide à éviter la dissémination des bacilles tuberculeux.

L'intervention terminée, la plaie sera inondée avec la solution de streptomycine.

L'avénement de la streptomycine et de l'acide para-aminosalicylique (PAS) dans le traitement de la tuberculose rénale a réduit la fréquence des fistules et de la dissémination miliaire fatale, à tel point, que la néphrectomie partielle pour tuberculose est maintenant praticable. Toutefois cette intervention n'est applicable qu'à quelques cas soigneusement sélectionnés.

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GASTROINTESTINAL CHANGES IN PNEUMOPERITONEUM[1]

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(Received for publication June 26, 1952)

INTRODUCTION

Pneumoperitoneum has been found to be of considerable value and it has assumed an important position in the nonsurgical treatment of tuberculosis. The use of pneumoperitoneum has increased much in recent years, and in this institution it is the most common form of collapse therapy.

In a recent study of pneumoperitoneum complications by one of the writers (I. D. B.), it was noted that approximately 60 per cent of the patients lost weight. Associated with the weight loss could be other gastrointestinal symptoms such as eructations, diarrhea, abdominal distress, pain, belching, and nausea. These complaints persisted usually for only short periods of time. In an occasional case, there was severe pain or gastrointestinal disturbance.

Gastrointestinal complications have been referred to in many papers dealing with pneumoperitoneum. Most of the writers consider these symptoms to be benign in character. Several investigators have associated the gastrointestinal complications in pneumoperitoneum with displacement of the abdominal viscera. However, the present writers have not seen any detailed reports of roentgenographic studies of the gastrointestinal tract made before and after induction of pneumoperitoneum. The object of the present investigation was to correlate the anatomic changes in the gastrointestinal tract as observed by radiological examination with symptoms and disturbances arising from pneumoperitoneum.

METHOD OF STUDY

A group of 37 patients (unselected, consecutive cases approved for pneumoperitoneum therapy) was included in this investigation. Roentgenographic studies of the gastrointestinal tract were made one or two days before initiation of therapy and were repeated six weeks and, again, six to eight months after induction. Films of the barium-filled stomach were taken in the erect position, using postero-anterior, lateral, and oblique views. Interval films of the abdomen were taken at one and three hours after ingestion of the barium to determine intestinal motility. The type, shape, and position of the stomach were noted at each examination. The widths of the cardiac and antral portions of the stomach were also measured. The position of the stomach was determined by measuring the distance on the postero-anterior film of the lowest portion of the stomach in relation to the iliac crest. Displacement of the stomach was noted by measuring the distance between the lowest portion of the stomach and the anterior margin of the lumbar spine in the lateral view. Finally, the symptoms and clinical findings of each patient during the first eight months of pneumoperitoneum were recorded and correlated with the roentgenographic data obtained.

OBSERVATIONS

Of the 37 patients, 12 were females and 25 were males; 18 were white and 19 Negro. Their ages varied greatly, with 19 patients who ranged from sixteen to

[1] From the Municipal Sanatorium of the City of New York, Otisville, New York (unit of the Department of Hospitals).

twenty-nine years, 14 from thirty to forty-nine years, and 4 more than fifty years of age.

A loss of weight occurred in 24 (65 per cent) of the group, a gain occurred in 12 (32 per cent), and one patient had an unchanged weight. In the majority of patients, particularly those with weight loss, the change in weight was six pounds or more.

Of the 37 patients, 12 (32 per cent) had no symptoms while 25 (68 per cent) had one or more complaints. The symptoms and the number of patients in whom they occurred were as follows: eructation, 8; anorexia, 7; diarrhea, 6; pain, 5; nausea, 4; belching, 3; flatulence, 1. The symptoms were uniformly mild or of short duration. Although weight loss could be associated with other symptoms and anorexia, it could also occur with no other obvious complaints.

The patients were divided into three groups according to the type of stomach found prior to pneumoperitoneum. In *Group A* were 4 patients with a *hyposthenic* stomach; in *Group B*, 7 with a *hypersthenic* type; and in *Group C*, 26 with a normal J-shaped, or *sthenic*, stomach.

The tone and type of stomach usually follows the habitus of the individual. The *hypersthenic* type of stomach (in the broad person) has a steer-horn shape with a wide cardiac contour tapering to the pylorus and is transverse and placed high in the abdomen. The *hyposthenic stomach* (in the thin, narrow person) is elongated, narrow, and low in position. As the lower pole sags down, the lumen there may be larger than elsewhere. The *sthenic* type (in normal habitus) is the normal J-shaped vertical stomach. The lower pole is about equal in diameter to the upper portion and is not very dependent.

Roentgenographic studies of the gastrointestinal tract before and after pneumoperitoneum showed changes which could be classified in the following categories: (*a*) shape of stomach, (*b*) position of stomach, (*c*) displacement of stomach, and (*d*) intestinal motility.

Shape of Stomach

Of the 4 hyposthenic stomachs, 3 remained unchanged while one assumed a sthenic appearance. In the 7 hypersthenic cases, 2 became sthenic and 2 hyposthenic while the rest were unchanged. Among the 26 sthenic patients, the stomach took on a flask shape with a long narrow neck and wide base in 13 while 8 remained sthenic in type, 4 became hyposthenic, and one became hypersthenic.

Actual measurement of the cardiac and fundal portions of the stomach before and after pneumoperitoneum revealed the typical changes to consist of elongation and narrowing of the cardia and widening of the fundus. The narrowing of the body of the cardiac end of the stomach occurred in 30 of 37 patients. It took place in all 4 hyposthenic patients but was only slight and not greater than one and one-half inches. The change was more marked in the other patients, with variations up to two and one-half inches, and occurred in 5 hypersthenic and 21 sthenic patients. This cardiac narrowing frequently reached its maximum early and usually within two months after pneumoperitoneum was initiated.

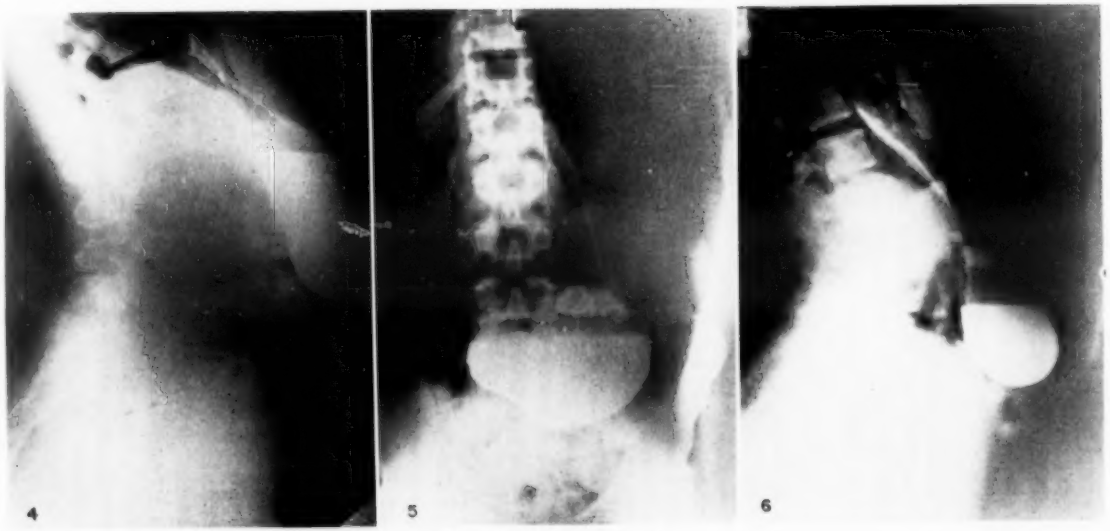
The fundus showed widening in 29 of the 37 cases (3 hyposthenic, 5 hypersthenic, and 21 sthenic patients). The change was slight in the hyposthenic and

FIGS. 1-3. *Case 1* (G. J.)

FIG. 1. April 18, 1950. Postero-anterior erect film of the barium-filled stomach taken previous to induction of pneumoperitoneum. Stomach is of the sthenic type. Width of the cardiac portion, 5 cm.; width of fundus, 5 cm. The lowest point of the stomach is 3 cm. above the iliac crest.

FIG. 2. April 18, 1950. A lateral view of the barium-filled stomach taken before induction of pneumoperitoneum. Posterior aspect of the stomach is 3 cm. anterior to the body of L3.

FIG. 3. June 14, 1950. Pneumoperitoneum induced April 20, 1950. Postero-anterior erect film seven weeks after induction. Width of the cardiac portion of the stomach is reduced to 2 cm. The lowest point of the stomach has dropped to 2 cm. below the iliac crest. The width of the fundus has increased to 7.5 cm. in diameter. The pneumoperitoneum compresses the cardiac portion of the stomach almost exclusively. Patient's weight unchanged. No gastro-intestinal symptoms are present.



FIGS. 4-6. *Case 1* (G. J.)

FIG. 4. June 14, 1950. Lateral film of stomach taken seven weeks after induction of pneumoperitoneum. There is increased anterior displacement of the stomach with its posterior aspect 6 cm. from the lower border of L4. The lowest point of the fundus is at the level of the superior aspect of L5.

FIG. 5. December 12, 1950. Postero-anterior view of stomach after eight months of pneumoperitoneum. There is now marked elongation and narrowing of the cardiac end which measures 1.2 cm. in diameter. The stomach is changed to a hyposthenic type. The lowest portion of the stomach is 8 cm. below the iliac crest. The fundus is dilated to 8 cm. in diameter. The bulk of the pneumoperitoneum compresses the upper two-thirds of the stomach, displacing it inferiorly. Loss of weight started in August, 1950. By December, 1950, the patient was fourteen pounds below pre-pneumoperitoneum weight. No gastrointestinal symptoms are present.

FIG. 6. December 12, 1950. Lateral view of the stomach eight months after induction of pneumoperitoneum shows further anterior displacement of the fundus, which is now 8 cm. anterior to the lower border of L5, and its lowest point is at the level of the promontory of the sacrum.

hypersthenic patients and did not measure more than one inch. The widening was more noticeable in the sthenic patients, with variations up to two and one-half inches. The widening of the fundus reached a maximum in many patients within two months after the start of therapy, but in approximately one-half of the group the widening was greater after six months of treatment.

The normal contour and position of the stomach before pneumoperitoneum are shown in figure 1. Figure 3 illustrates slight narrowing and lengthening of the cardiac part of the stomach and widening of the fundal portion after six weeks of therapy. Figure 5 demonstrates marked elongation and narrowing of the cardiac end of the stomach and considerable fundal widening (the stomach now flask-shaped) after eight months of pneumoperitoneum.

Position of Stomach

A characteristic change with pneumoperitoneum was a drop of the stomach. After six weeks of therapy, this had occurred in 19 of the patients (4 hyposthenic, 5 hypersthenic, and 10 sthenic), but the position was unchanged in 5 while in 13 patients it was at a level slightly higher than before treatment. The drop was usually considerable with variations up to three and one-half inches. After six months of therapy, in some patients the stomach drop was accentuated, but in others the stomach was at a higher level. Thus, the proportion of patients with a change in position of stomach (elevation or drop) was about the same as after a short period of pneumoperitoneum. Figure 3, as compared with figure 1, shows a slight drop of the stomach after six weeks of pneumoperitoneum. A marked stomach drop with continuation of therapy is illustrated in figure 5.

Displacement of Stomach

An anterior displacement of the axis of the stomach took place uniformly soon after induction of pneumoperitoneum. Thus, after six weeks of therapy this had occurred in 33 of 37 patients (2 hyposthenic, 7 hypersthenic, and 24 sthenic patients). In 3 patients there was no change while one showed posterior displacement. The anterior movement varied from one-half inch to three and one-half inches (in most instances, less than one and one-half inches).

As pneumoperitoneum was continued, alterations in position of the stomach took place. Although in most cases the stomach was still in an anterior location, a backward movement occurred in 10 patients. This change varied from one-half inch to two inches, and in some patients the stomach assumed a position similar to that before pneumoperitoneum.

The normal position of the stomach in relation to the spine is shown in figure 2. The anterior displacement of the stomach after six weeks of pneumoperitoneum is shown in figure 4. Figure 6 indicates that after eight months of treatment the anterior displacement has increased.

Intestinal Motility

Soon after pneumoperitoneum was initiated, changes in intestinal motility were noted but there was no significant tendency in this respect. After six weeks

of treatment, 12 patients had increased motility and an equal number showed decreased motion. As pneumoperitoneum was continued, intestinal motility would change again in some cases but for the total group the proportion of patients with altered motility remained about the same, with only a slightly higher ratio of patients with increased motion.

DISCUSSION

The typical or characteristic anatomic changes occurring with pneumoperitoneum included the following: elongation and narrowing of the cardiac portion of the stomach, widening or dilatation (and atonicity) of the fundus, anterior displacement and a drop of the stomach.

When the pneumoperitoneum is initiated, the air first collects on the superior, anterior, and lateral surfaces of the stomach. Thus, some narrowing of the cardiac end can take place while the remainder of the stomach is still not influenced much by the air (figure 3). As the pneumoperitoneum space enlarges, the air compresses the entire length of the stomach. Lengthening and narrowing of the stomach ensues and a drop of the organ occurs (figure 5). The air is now present above, on the sides of, anteriorly and posteriorly to, the stomach. The displacement of the stomach will depend on the pressure of the air on a particular surface. Thus, with the air posteriorly, the stomach can be pushed forward and also upward but, with much anterior air, it can be moved or compressed backward and downward.

With pneumoperitoneum, the abdominal organs are compressed or pushed downward toward the pelvis. The maximum amount of air is in the upper abdomen and under the diaphragms. The compressed organs form a large triangular shadow with the liver (and right kidney) forming the right side, the spleen (and left kidney) the left side, the stomach in the apex of the triangle, and the remainder and main portion of the body of the triangle composed of intestines.

Not every pneumoperitoneum results in a typical flask-shaped stomach. The viscus may be elongated and tubular without much dilatation of the fundus or marked narrowing of the cardia. There also may be no considerable displacement or drop of the stomach. The stomach may be elongated and yet, because of its displacement forward and upward, it may be higher with pneumoperitoneum than without it.

In many cases, particularly the hyposthenic and hypersthenic, the maximum anatomic changes were achieved early, after approximately six weeks of pneumoperitoneum. As pneumoperitoneum was continued, there was little additional or progressive alteration because adjustment to the air apparently took place. However, later changes in position and shape of the stomach could occur as noted in the sthenic cases.

There was little correlation between the anatomic alteration achieved by pneumoperitoneum and the gastrointestinal symptoms. Thus, in the patients without symptoms there were slight, moderate, or marked pneumoperitoneum spaces. Likewise, all variations of collapse were present in the patients with symptoms. In the symptomatic cases, however, there was a higher proportion of pneumoperitoneum of good anatomic extent.

The studies of intestinal motility provided some answer to the greater incidence of diarrhea in the patients with pneumoperitoneum. Constipation was not presented as a disturbing symptom although it can occur.

Variations in the appearance of the stomach with pneumoperitoneum could be due to different factors. In the hyposthenic patient with the viscus pendulous, long, and narrow to start with, only a small drop occurred and also slight changes in the cardia and fundus. The musculature and tightness of the abdominal wall are important. With a lax abdomen, the air forces out the abdominal wall and exerts less pressure on the stomach. With a tight abdominal wall, the tone of the abdominal muscles will help the air push the stomach and organs down. The position of the stomach is related also to the presence of fluid in the pneumoperitoneum space. In 5 cases, abdominal fluid floated and raised the stomach. In these instances, the stomach reverted to a more normal position and shape with diminution or elimination of the cardiac narrowing, fundal dilatation, and viscus drop. The drop of the stomach may be related to the position of the liver. As the liver moves down, it can exert pressure on the stomach. The liver and spleen may be broadly adherent to the diaphragm or there may be restricting adhesions between these organs and the diaphragm. This may interfere with an effective pneumoperitoneum and limit the elevation of the diaphragms and movement of the abdominal organs. Finally, in one patient with marked lordosis of the lumbar spine, there was an unusual forward position of the stomach (which almost touched the anterior abdominal wall), with air located mainly superiorly and laterally.

SUMMARY

A group of 37 patients with pneumoperitoneum had gastrointestinal studies performed immediately before initiation of therapy and again after six weeks and six to eight months of collapse treatment. The typical anatomic changes which occurred with pneumoperitoneum included elongation and narrowing of the cardiac portion of the stomach, widening or dilatation of the fundus, anterior displacement and a drop of the stomach. The factors which might influence these alterations have been discussed. The majority of patients lost weight with pneumoperitoneum. Other gastrointestinal symptoms were usually mild. There was little correlation between the symptoms which occurred with pneumoperitoneum and the degree of anatomic changes.

SUMARIO

Las Alteraciones Gastrointestinales en el Neumoperitoneo

En un grupo de 37 enfermos tratados con el neumoperitoneo, hiciéronse estudios gastrointestinales inmediatamente antes de iniciar la terapéutica y de nuevo a las seis semanas y a los seis a ocho meses de la colapsoterapia. Las típicas alteraciones anatómicas que ocurrieron con el neumoperitoneo comprendieron alargamiento y estrechamiento de la porción cardíaca del estómago, ensanchamiento o dilatación del fondo y desplazamiento anterior y ptosis del estómago. Discútense los factores que podrían afectar tales cambios. La mayoría de los enfermos neumoperitoneizados perdieron peso. Otros síntomas gastrointestinales fueron leves por lo general. Hubo poca correlación entre los síntomas subsiguientes al neumoperitoneo y la intensidad de las alteraciones anatómicas.

RESUME

Altérations gastro-intestinales dans le pneumopéritoine

Dans un groupe de 37 malades porteurs d'un pneumopéritoine, des études gastro-intestinaux ont été pratiquées immédiatement avant l'initiation de la thérapie, puis au bout de six semaines et de six à huit mois de traitement par le collapsus. Les modifications anatomiques spécifiques, qui sont survenues à la suite du pneumopéritoine, comprenaient l'élongation et le retrécissement de la zone du cardia, l'élargissement ou la dilatation du corps, le déplacement antérieur et la ptose de l'estomac. Les facteurs susceptibles d'influencer ces altérations ont été étudiés. La majorité des malades a perdu du poids avec le pneumopéritoine. Les autres symptômes gastro-intestinaux étaient habituellement légers. Il y avait peu de corrélation entre les symptômes associés au pneumopéritoine et le degré des modifications anatomiques.

REFERENCE

(1) Bobrowitz, I. D.: Complications of pneumoperitoneum therapy, Dis. of Chest (to be published).

STUDIES ON THE GROWTH OF MYCOBACTERIA[1, 2]

I. The Occurrence of Arithmetic Linear Growth

MYRON W. FISHER[3] AND WALDEMAR F. KIRCHHEIMER

(Received for publication June 12, 1952)

INTRODUCTION

In a previous publication (1), the expression "arithmetic linear growth" was proposed to describe a definite phase of the growth of *Mycobacterium tuberculosis* which was observed regularly when this organism was cultivated in liquid media with or without dispersing agents. During this growth phase, the increase in bacterial density existed as a straight line function of time, and it followed a typical logarithmic growth phase. Under the conditions described, this arithmetic linear, post-logarithmic growth continued for twelve days; following this, the organisms apparently entered into the stationary phase.

As mentioned in the previous paper (1), the occurrence of an arithmetic linear growth phase was not restricted to *M. tuberculosis* var. *hominis* but also characterized the growth of other mammalian varieties as shown by some preliminary studies. It was therefore of interest to carry out growth studies on additional species and strains of *Mycobacteria*, primarily to determine if arithmetic linear growth was a characteristic of representative members of the genus *Mycobacterium* cultivated in liquid media.

MATERIALS AND METHODS

The following is a list of the organisms included in this study and their respective sources:

M. tuberculosis var. *hominis*, H37Rv (Mr. W. Steenken, Jr., Trudeau Laboratories)
M. tuberculosis var. *hominis*, H37Ra (Mr. W. Steenken, Jr., Trudeau Laboratories)
M. tuberculosis var. *bovis*, Ravenel (Dr. W. H. Feldman, Mayo Foundation)
M. tuberculosis var. *bovis*, BCG (Dr. S. Rosenthal, Tice Laboratories)
M. avium (Dr. W. H. Feldman, Mayo Foundation)
M. avium, Kirchberg (Dr. W. H. Feldman, Mayo Foundation)
M. ulcerans (Dr. A. Karlson, Mayo Foundation)
M. ranae (Dr. J. D. Aronson, Henry Phipps Institute)
M. thamnopheos (A.T.C.C.[4] #4445)
M. marinum (A.T.C.C. #927)
M. lacticola (A.T.C.C. #9626)
M. phlei (A.T.C.C. #10142)
M. smegmatis, 54 (Dr. E. B. Tilden, Northwestern University)
M. smegmatis, 4172-101 (Dr. A. Karlson, Mayo Foundation)
M. smegmatis, 4172-101, streptomycin-resistant (Dr. A. Karlson, Mayo Foundation)

The culture medium had the following composition: asparagine, 0.5 per cent; potassium

[1] From the Department of Bacteriology, Northwestern University School of Medicine, Chicago, Illinois.

[2] Supported, in part, by a grant from Parke, Davis & Company; and, in part, by a research grant from the National Institutes of Health, Public Health Service.

[3] Present address: Research Laboratories, Parke, Davis & Company, Detroit, Michigan.

[4] American Type Culture Collection.

sulfate, 0.05 per cent; magnesium citrate, 0.15 per cent; and Tween 80,[5] 0.02 per cent. The pH was adjusted to 6.8 to 7.0 with 40 per cent sodium hydroxide and, following autoclaving, filtration-sterilized bovine albumin (fraction V, Armour) and glucose were added to give a final concentration of 0.2 and 0.5 per cent, respectively. This medium was dispensed in 7.0 ml. amounts in aluminum-capped round cuvettes (Coleman "7-304") externally measuring 19 by 150 mm. The inocula used were obtained from cultures in the above medium. In the case of the mammalian and avian strains, the inocula were taken from seven- or eight-day-old cultures, and in the case of the remaining cultures, inocula were taken from two-day-old cultures. Quadruplicates of the medium in cuvettes were inoculated for each strain with 0.2 ml. of undiluted bacterial suspension.

Cultures were incubated in an upright position in either an air incubator or in a constant temperature water bath. The incubation temperature was 37.5°C. for all strains except the following: the two strains of *M. avium* at 39.0°C., *M. thamnopheos* and *M. marinum* at 25.0°C.,

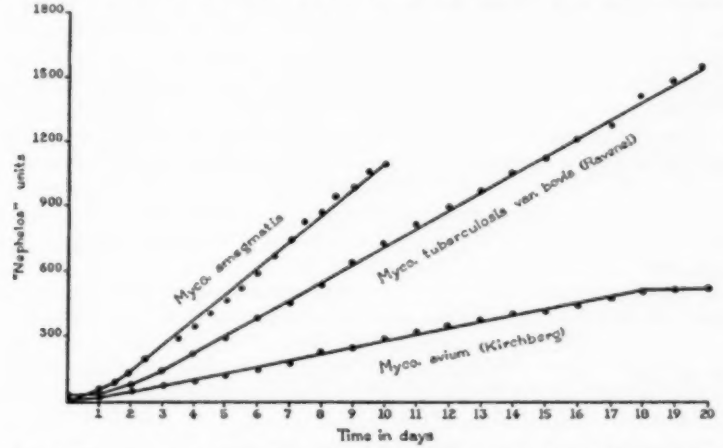


FIG. 1. The growth of mammalian, avian, and saprophytic strains of the genus *Mycobacterium* in a liquid medium containing Tween 80.

and *M. ulcerans* at 32°C. Growth was measured turbidimetrically, using the Coleman model 7 photonephelometer, at either twelve- or twenty-four-hour intervals, depending on the rate of growth of the particular strains. Prior to each determination, the cuvettes were well shaken so that smoothly turbid suspensions were obtained. For each strain, growth studies were performed at least twice, and replicate experiments yielded closely comparable results in all cases.

RESULTS

Under the conditions described, all of the 15 strains of *Mycobacteria* which were employed consistently exhibited the same type of growth curve, namely, a logarithmic growth phase followed by a relatively long arithmetic linear phase. An example of the kind of growth pattern which was observed is illustrated on the

[5] Proprietary name of polyoxyethylene derivative of Sorbitan monooleate, Atlas Powder Co., Wilmington, Delaware.

graph in figure 1 for a mammalian strain (*M. tuberculosis* var. *bovis*, Ravenel), an avian strain (*M. avium*, Kirchberg), and a saprophytic strain (*M. smegmatis*, 54). This graph was plotted with arithmetic values and divisions for both time and bacterial density, with the latter expressed as "nephelos" units on the ordinate. With the photonephelometer, cuvettes, and culture medium employed, it has been determined (2) that one "nephelos" unit corresponds to approximately 500,000 tubercle bacilli per ml.

DISCUSSION

The results of the present study establish that a prolonged arithmetic linear growth phase occurred with all of the 15 strains of *Mycobacteria* which were studied. These strains represent the main categories and most of the species of the genus *Mycobacterium* which are cultivable: namely, the mammalian, avian, cold-blooded, and saprophytic types. This would suggest that arithmetic linear growth under the described conditions is at least a characteristic of the genus. Whether or not this could be a taxonomic or identifying criterion remains to be determined since there is insufficient evidence regarding the nature of the post-logarithmic phases of the growth curves of nonacid-fast bacteria. However, studies in this laboratory with *Micrococcus pyogenes* var. *aureus*, *Streptococcus faecalis*, *Bacillus subtilis*, *Aerobacter aerogenes*, and *Escherichia coli* grown in "non-synthetic" liquid media have failed to reveal the presence of an arithmetic linear growth phase (2). In addition, the growth of *E. coli* in a synthetic medium follows the usual type of curve and does not exhibit an arithmetic linear growth phase (3). Of greater importance, potentially, than that of mere classification is the implication that the characteristic of arithmetic linear growth may be associated with the factors responsible for the relatively slow growth of *Mycobacteria*. Thus, this linear growth phase, in addition to the logarithmic phase, may provide a basis for elucidation of some fundamental physiologic properties of *Mycobacteria* that distinguish them from other microorganisms.

Because a straight line relationship exists between time and bacterial concentration in the arithmetic linear phase, this phase could be used for quantitative growth studies. In such cases, a "growth rate" could be determined which would be an expression of a constant cell mass increase per unit time. If such data are used, care should be exercised to distinguish these from growth rate constants or generation times obtained from results in the logarithmic phase. The use and interpretation of growth rates obtained from the arithmetic linear phase would be limited at the present time since the factors responsible for the institution of arithmetic linear growth are not yet known. Indeed, results of some preliminary experiments indicate that the relative rates of growth in the logarithmic and arithmetic linear phases may vary independently, particularly with the mammalian strains. As an over-all generalization, it can be concluded from the data that the so-called "rapidly-growing" *Mycobacteria* are such because they grow more rapidly in both the logarithmic and arithmetic linear phases than do the mammalian strains.

SUMMARY

Turbidimetric growth studies were performed on 15 strains of *Mycobacteria*, representing the mammalian, avian, cold-blooded, and saprophytic types. It was determined that a relatively long arithmetic linear growth phase directly followed the logarithmic phase with all strains.

The possible usefulness of the arithmetic linear growth phase as a quantitative tool for growth studies is discussed. The occurrence of such growth also may be a specific characteristic of the organisms of the genus *Mycobacterium*.

SUMARIO

Estudios de la Proliferación de las Micobacterias: 1. Ocurrencia de Crecimiento Lineal Aritmético

Ejecutáronse estudios turbidimétricos del crecimiento en 15 cepas de *Mycobacteria*, que representaban las formas manífera, aviaria, hemacrima y saprofita. Determinóse que, en todas las cepas, la fase logarítmica iba directamente seguida de una fase relativamente larga de crecimiento lineal aritmético.

Discútese la posible utilidad de la fase lineal aritmética del crecimiento como instrumento cuantitativo para estudios del crecimiento. La ocurrencia de tal crecimiento quizás sea también una característica específica de los microbios del género *Mycobacterium*.

RESUME

Etudes sur la croissance des Mycobacteria: I. L'occurrence de la croissance arithmétique linéaire

Des études turbidimétriques sur la croissance ont été effectuées sur 15 souches de *Mycobacteria* représentant le type mammifère et le type aviaire, celui des animaux à sang froid et les saprophytes. Il a été déterminé qu'avec toutes les souches une phase arithmétique linéaire, relativement longue, de la croissance succédait directement à la phase logarithmique.

L'utilité possible de la phase arithmétique linéaire de la croissance comme instrument de mesure quantitative pour les études de croissance est étudiée. Cet aspect de la croissance pourrait être également une caractéristique spécifique des organismes du genre *Mycobacterium*.

REFERENCES

(1) Fisher, M. W., Kirchheimer, W. F., and Hess, A. R.: The arithmetic linear growth of *Mycobacterium tuberculosis* var. *hominis*, J. Bact., 1951, *62*, 319.

(2) Fisher, M. W.: The turbidimetry of bacterial and mycobacterial suspensions, Doctorate dissertation, Northwestern University, 1951.

(3) Fisher, M. W.: Unpublished data.

Notes

THE VALUE OF ABSORPTION IN SEROLOGIC TESTS FOR TUBERCULOSIS

A new serologic test for tuberculosis was reported by the writers[1] in which a preliminary procedure for excluding all of the nonreacting blood specimens was described. When a group of 464 specimens of blood was tested by this method with the routine antigen[2], approximately 34 per cent of the specimens reacted. Investigation of the persons whose blood reacted in the serologic test for tuberculosis failed in most instances to give a history or clinical or roentgenographic evidence of pulmonary tuberculosis. One hundred and seventy-eight sera of this group were also treated in the same manner but with another antigen[3], and 33, or 19 per cent, reacted. Twenty-six specimens gave a titer of 1, and titers of 2, 3, and 5 were obtained with the remaining 7 specimens. It seems, therefore, that until more satisfactory antigens become available some other approach to the problem is necessary. Such an approach is desc ibed in the present report.

A mixed culture of *Staphylococcus albus* and *Staphylococcus aureus* grown in beef broth was inoculated into 16-ounce Blake bottles containing beef infusion agar and was incubated at 37°C. from forty-eight to seventy-two hours. Into each bottle, 15 ml. of sterile saline were added and the growth was loosened with a scraper. The suspension was transferred to 100 ml. bottles. The bottles containing the suspension of the organisms were placed in an autoclave at 115° to 118°C. for twenty minutes. After the bottles were cooled, the suspensions were poured into watch glasses and allowed to stand in an incubator at 48°C. until the fluid was completely evaporated. The dried organisms were then scraped off the watch glass and collected in a Petri dish. The tubercle bacilli were grown on Löwenstein medium from three to nine weeks, and were processed in the same manner as the *Staphylococci*. The serum to be retested was inactivated at 56°C. for one-half hour and was absorbed with sheep cells. All sera which reacted in the preliminary test were treated as follows: 50 to 60 mg. of dried organisms were added to 1 ml. of serum. The inoculated serum was shaken in a shaking machine for twenty minutes and then allowed to stand in the refrigerator at 4° to 6°C. overnight. The specimen was centrifuged at 2,000 r.p.m. for five minutes and the clear serum was separated from the packed microorganisms. The tests were performed in triplicate with unabsorbed serum, serum absorbed with *Staph. albus* and *Staph. aureus*, serum absorbed with tubercle bacilli. The technique of the test is the same as that described in the previous paper except that two units of complement instead of one were used as a control because of the anticomplementary property of the patient's serum. The serum was in some instances absorbed twice with the *Staphylococci* in order to effect complete absorption of substances unrelated to tuberculosis.

Ninety-two reacting sera from patients with clinical and laboratory evidence of tuber culosis were absorbed with dried cultures of a pathogenic tubercle bacillus. These reacting sera when tested after absorption with a dried culture of a pathogenic tubercle bacillus failed to react in the test. Two hundred and thirty reacting sera from 735 persons without clinical or roentgenographic evidence of tuberculosis were treated in the same manner

[1] MAILLARD, E. R., AND GAGLIARDO, F. J.: Am. Rev. Tubere., 1951, *64*, 675.

[2] Concentrated tuberculin (four times international standard) kindly supplied by Dr. D. Piersma, Director, Human Biology Section, Lederle Laboratories, Pearl River, New York.

[3] Kindly supplied by Dr. Mary Pangborn, New York State Division of Laboratories and Research, Albany, New York.

and, when retested, also failed to react in the test. Reacting sera from both of these groups of donors, that is, the 92 with evidence and the 230 without evidence of pulmonary tuberculosis, were further absorbed with dried cultures of *Staph. albus* and *Staph. aureus*. The

TABLE 1

SERA FROM 34 OF THE 92 TUBERCULOUS DONORS

NUMBER OF SPECIMENS	1*	1	6	1*	5	1*	3	1	2	1	1	4	2	1	1	1	2
Before absorption	250	120	50	50	40	40	33	33	25	20	17	12	10	8	7	5	4
Absorbed with tubercle bacillus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Absorbed with *Staphylococci*	170	120	50	33	40	20	33	25	20	17	12	10	7	5	3	3	3

* Titers appreciably lower after absorption with *Staphylococci*.

TABLE 2

RESULTS OF SEROLOGIC TEST ON SPECIMENS FROM TUBERCULOUS AND NONTUBERCULOUS DONORS

DONORS	NUMBER OF SPECIMENS	NUMBER NOT REACTING	NUMBER REACTING BEFORE ABSORPTION WITH STAPHYLOCOCCUS	NUMBER REACTING AFTER ABSORPTION WITH STAPHYLOCOCCUS
Nontuberculous	735	505	230	11
Tuberculous	92	0	92	92

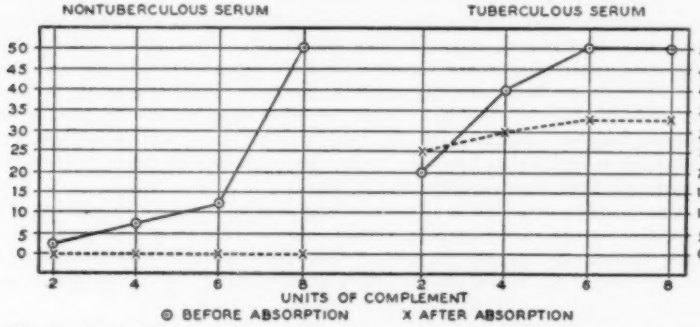


FIG. 1. Sera from tuberculous and nontuberculous donors tested with two to eight 50 per cent units of complement before and after absorption.

sera from the 92 tuberculous patients still reacted after absorption with *Staph. albus* and *Staph. aureus*, while all but 11 of the sera from the 230 nontuberculous donors failed to react when retested. To recapitulate, the reacting sera from tuberculous and nontuberculous patients failed to react after absorption with a dried culture of a pathogenic tubercle

bacillus; the sera from the tuberculous patients and 11 of the sera from the nontuberculous donors continued to react after treatment with *Staph. albus* and *Staph. aureus*. Sera from a few of the tuberculous patients when tested after absorption with *Staph. albus* and *Staph. aureus* gave appreciably lower titers. Sera from 3 of the 11 nontuberculous donors gave titers of 7, 10, and 40 before absorption with *Staph. albus* and *Staph. aureus* and after absorption the titers were 2, 5, and 10, respectively. The 3 specimens were tested with 4, 6, and 8 units of complement, and the titers obtained with each serum and different amounts of complement were approximately the same. There is no history or clinical or roentgenographic evidence of the presence of tuberculosis in these 3 patients. One patient did have an upper respiratory infection, however, at the time the specimen was collected. The remaining 8 are still being investigated for evidence of tuberculosis. It was apparent from these observations that all reacting sera should be absorbed by the *Staph. albus* and *Staph. aureus* in order to determine whether any or all of the reacting substances in the blood are tuberculous antibodies (tables 1 and 2).

It was previously demonstrated by the writers[4] that, in a quantitatively standardized test, maximum reactions with tuberculous anti-serum occurred in the presence of an optimum amount of complement which was determined to be four 50 per cent units. It was further demonstrated that complement in excess of this amount did not appreciably change the titer of the reacting serum. This phenomenon was applied to the reacting sera and it was demonstrated again that, when the reacting substance was not removed or partly removed by the *Staph. albus* and *Staph. aureus*, the titer of the absorbed portion of the serum remained appreciably the same when tested with amounts of complement in excess of the optimum. Whereas, when the reacting substance could be removed by the *Staph. albus* and *Staph. aureus*, the unabsorbed portion of the serum showed a rise in the titer when tested with amounts of complement in excess of the optimum four units (figure 1).

It is apparent from these studies that substances are present in the sera of some tuberculous and nontuberculous persons which react with the antigen routinely used in serologic tests for tuberculosis and which may or may not be related to tuberculosis. It has been demonstrated that these substances may be differentiated into those which are tuberculous antibodies and those which are unrelated to tuberculosis. This has been accomplished first by absorption of the sera with dried cultures of *Staph. albus* and *Staph. aureus*, which remove the substances unrelated to tuberculosis without affecting the tuberculous antibodies. Second, when the antibodies are tuberculous, the titer remains the same when tested with four, six, and eight 50 per cent units of complement. In contrast, when the substance is unrelated to tuberculosis, the titer increases when tested with amounts of complement larger than the optimum four units.

In summary: It is now possible to screen a large number of persons for evidence of tuberculosis by a preliminary serologic procedure which tests one amount of serum. The diagnostic significance of any reacting serum can be further determined by absorption with *Staph. albus* and *Staph. aureus* and by testing the serum with varying amounts of complement.

Division of Laboratories and Research
Nassau County Department of Health
Hempstead, New York

Edgar R. Maillard
Frank J. Gagliardo

May 8, 1952

[4] Maillard, E. R.: Am. J. Pub. Health, 1952, *42*, 175.

Correspondence

EFFECT OF IODINE ON TUBERCULOSIS

In November, 1951, Dr. John R. Mote had occasion to write to approximately twenty students of tuberculosis in this country requesting their opinion on the possible effects of iodine on tuberculosis. Late in the spring of 1952, the collected replies were circulated to the men who had been queried, and the Editor of the REVIEW *happened to have the opportunity to see the collection. It occurred to him that the fact that such a distinguished panel of investigators should independently state that there was so little satisfactory information on the subject was in itself information of sufficient value to warrant publication. Accordingly, through the courtesy of Dr. Mote and the individual writers, who have good-naturedly given permission to publish what was, in fact, their private correspondence, the* REVIEW *is enabled to publish the replies below. The only deletions or insertions are indicated, respectively, by . . . or brackets. These were all made by the Editor and were used solely where statements were not germane to the present purpose. It is believed that the opinions of the various letter writers taken together constitute an impressive collection, the publication of which might stimulate thought and study of the subject.*

September 20, 1952 *The Editor*

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
66th STREET and YORK AVENUE
NEW YORK 21, N. Y.

November 23, 1951

Dear Dr. Mote:

I do not have the background to express a responsible opinion concerning the effect of iodides in human tuberculosis.

I know of no indication that these substances can stimulate the growth of tubercle bacilli or favor them by any direct action on them. There have been vague reports that iodides may activate the proteolytic enzymes of the plasma and thereby contribute to the liquefaction of fibrin. I do not know of any evidence that this activation of fibrinolysis can have any unfavorable effect in human tuberculosis.

Sincerely yours,
R. Dubos (Signed)
René J. Dubos

RJD:j

VETERANS ADMINISTRATION HOSPITAL
54th STREET AND 48th AVENUE SOUTH
MINNEAPOLIS 17, MINNESOTA

November 23, 1951
IN REPLY REFER TO: 5106-10EE

Dear Dr. Mote,

In reply to your letter of November 20, as to the potential harmfulness of [iodine in tuberculosis], I am unable from personal experience to give you more than clinical impressions, which are to the effect that small quantities of iodides, in the range of the dosage

you mention, given for short periods of time, apparently do not harm patients with tuberculosis. On the other hand, in one patient whom we have had, who had both coccidioidomycosis and tuberculosis simultaneously, when massive doses of potassium iodide were given for the coccidioidomycosis, there was questionable evidence as to the unfavorable effect upon his tuberculosis. This case was published in the *American Review of Tuberculosis*, vol. 59, no. 4, 415–428 (April), 1949.

I agree with you that the older literature on the effect of iodides on tuberculosis is of relatively little value. Perhaps you are aware of a study done at Vanderbilt of iodide and streptomycin therapy in pulmonary tuberculosis. A progress report on this study appears in the *Transactions* of the Ninth Conference on the Chemotherapy of Tuberculosis (p. 232). I do not know if the later results have been published elsewhere.

Perhaps you are also aware that at the University of Colorado a study is being pursued of the effects of potassium iodide on experimental tuberculosis in animals, which I understand is leading to somewhat contrary conclusions from that of the Vanderbilt study. It is possible that Dr. Waring will in his reply to your letter comment upon this. These two are the only current studies on this subject of which I am aware, and I must admit that at the present time the picture is unclear. I do believe however that there is some evidence, however tenuous, which indicates caution about the use of "excessive" amounts of iodine in the presence of tuberculosis, but I do not have the faintest idea as to what is "excessive." I trust that these few comments will be of some value to you.

Sincerely yours,
William B. Tucker (Signed)
William B. Tucker, M.D.
Chief, Tuberculosis Service

VETERANS ADMINISTRATION
WASHINGTON 25, D. C.

November 26, 1951

DEPARTMENT OF
MEDICINE AND SURGERY

IN REPLY REFER TO: 10EE

My dear Dr. Mote:

. . . . . .

The only work I know to be remotely connected with the subject is that of Robert Goodwin *et al.* (Veterans Administration Hospital, Nashville) and Cajori-Sabin (which you should hear of through Jim Waring). Both of these groups used iodides in conjunction with streptomycin in the treatment of tuberculosis. There is, in both, the fundamental assumption that the iodides will "dissolve" granulation tissue and free tubercle bacilli.

This assumption used to be stated to me as a fact when I was in medical school. But, curiously enough, I do not know upon what evidence the fact is based. It would certainly seem unlikely to me that 0.2 gm. for "a few days" would have such an effect.

Better luck elsewhere.

Sincerely yours,
Arthur Walker (Signed)
Arthur M. Walker, M.D.
Secretary, Committee on
Streptomycin

DUKE UNIVERSITY
DURHAM
NORTH CAROLINA

November 26, 1951

School of Medicine
Department of Medicine

Dear Dr. Mote:

Thank you for your recent information as well as query. The question posed is difficult or impossible to answer at the moment. You are familiar with the factual data behind this fear and the studies of Dr. Avery in *Science* on the use of iodides and streptomycin. There is little factual material on the effect of iodides on the lesion.

The evidence will have to be considerably better than that at hand before one can say that iodides have any effect on latent tuberculosis or a deleterious effect on active tuberculosis. The problem posed by your material is no greater than the widespread use of iodides in asthma as an expectorant and thus it would not seem to be a contraindication to the use of these materials. It would seem that this could be answered by studying the effect of your material in a relatively resistant animal like the rabbit infected with H37Rv.

. . . . . .

I am very sorry that I can be of no help to you in answering your question.

Sincerely,
Samuel Martin (Signed)
Samuel P. Martin, M.D.

SPM:riw

UNIVERSITY OF WASHINGTON
SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE
SEATTLE 5

November 26, 1951

Dear Dr. Mote:

. . . . . .

I have had no personal experience with iodides in tuberculosis and therefore do not feel that I can authoritatively state whether your preparation is likely to be deleterious or not. As you are undoubtedly well aware, animal studies in the past years have demonstrated the breakdown of caseous lesions with iodides, and this has even been used therapeutically in conjunction with streptomycin in order to give better penetration. What you want, of course, is a preparation which can be used with impunity, whether the patient is getting streptomycin or not. I am sorry I cannot be more dogmatic in my judgment of this situation.

. . . . . .

Very sincerely yours,
William Kirby (Signed)
William M. M. Kirby, M.D.

WMMK:mr

MAYO CLINIC
ROCHESTER, MINNESOTA

November 27, 1951

Dear Doctor Mote:

Your letter of November 20, regarding the effect of iodine on tuberculosis, has been received. I have been aware of the fact that there was no adequate study of this problem available in the recent literature and have been hoping that someone would investigate it.

It has been my clinical opinion that doses of iodine of the order mentioned in your letter [i.e., 100 to 200 mg. daily] are of no danger and have not hesitated to prescribe iodine to patients with tuberculosis whenever there was a real indication for this medication.

I shall be very anxious to learn the results of your survey and will look forward to hearing from you about it.

Yours very truly,
David T. Carr (Signed)
David T. Carr, M.D.

DTC/ltd

DUKE UNIVERSITY
DURHAM
NORTH CAROLINA

November 27, 1951

School of Medicine
Department of Bacteriology

Dear Dr. Mote:

In answer to your letter of November 21 I would say that I have seen one child where there was a spread of the pulmonary tuberculosis and the development of active symptoms following the administration of potassium iodide under the mistaken impression that the patient had blastomycosis.

It is my impression that potassium iodide may be dangerous when given to a patient with tuberculosis, if the patient has a marked positive skin test to tuberculin but would be harmless or actually useful in patients who have no excess sensitivity.

Very sincerely yours,
David T. Smith (Signed)
David T. Smith, M.D.

TDS/ms

VETERANS ADMINISTRATION HOSPITAL
SUNMOUNT, NEW YORK

November 27, 1951
IN REPLY REFER TO: 5096-10EE

Dear Dr. Mote:

I have your inquiry regarding the possible dangers of iodides in human tuberculosis.

I must say that I have had no personal experience in the use of these, and cannot con-

tribute any real information to the query. I am aware of the traditional contraindications to iodine in tuberculosis; but I have always assumed that these were statements of opinion based upon clinical observation. In view of the variability and unpredictability of pulmonary tuberculosis, I would be inclined to dismiss such observations, especially in the absence of confirmatory studies in experimental tuberculosis.

I certainly would not hesitate to use a preparation containing 100–200 mgms of iodine in active pulmonary tuberculosis, just as we do not hesitate to use iodine preparations for bronchography, angiography or pyelography.

Sincerely,
Nicholas D. D'Esopo (Signed)
Nicholas D. D'Esopo, M.D.
Chief, Tuberculosis Service

UNIVERSITY OF MICHIGAN
ANN ARBOR

November 27, 1951

UNIVERSITY HOSPITAL
DEPARTMENT OF IETERNAL MEDICIEE
Cyrus C. Sturgis, M.D.
Professor of Medicine

Dear Doctor Mote:

I have your letter of November 20, 1951 regarding the question of danger of the iodine in [tuberculosis]. There have been no convincing controlled studies of the effect of iodides in tuberculosis on either side of the question, in my opinion. There are, however, a number of cases, in which unexpected positive sputum and/or spread of disease coincided with the administration of iodides. My opinion would have to be stated something in this fashion. I doubt that 100–200 mg. of iodine per day for a brief period would be at all harmful to patients with tuberculosis. Since I do not know, however, I would be unwilling to give iodides to patients with tuberculosis, unless it was unavoidable. I can see no reason taking even a theoretical risk, unless one has *something* to gain from it.

I would appreciate learning the opinion of your other consultants.

Sincerely yours,
John Adcock (Signed)
John Adcock, M.D.

JA:cf

H. CORWIN HINSHAW, M.D.
490 POST STREET
SAN FRANCISCO 2, CALIFORNIA

November 29, 1951

Dear Doctor Mote:

I am glad to reply to your request for an opinion concerning the possible harmful effect of iodides in pulmonary tuberculosis. . . . There is in my opinion no acceptable evidence that iodides have a deleterious effect on either experimental or clinical tuberculosis. In

days when iodides were commonly used in treatment of syphilis, I have seen such treatment carried out for very prolonged periods in patients who had both syphilis and tuberculosis, and without any suggestion of deleterious effect upon the tuberculous disease.

It is barely possible that the expectorant effect of iodides might by thinning the bronchopulmonary secretions facilitate the bronchogenic spread of tuberculous infection from one segment or lobe of the lung to another. This mechanism is, however, quite improbable or at least would rarely be operative. . . .

. . . . . .

Very truly yours,
H. C. Hinshaw (Signed)
H. Corwin Hinshaw, M.D.

HCH:IS

THE UNIVERSITY OF PENNSYLVANIA
THE HENRY PHIPPS INSTITUTE
for the
STUDY, TREATMENT AND PREVENTION OF TUBERCULOSIS
SEVENTH AND LOMBARD STREETS
PHILADELPHIA 47

November 29, 1951

Dear Dr. Mote:

This is in reference to your inquiry in regard to [iodine in tuberculosis]. . . .

There are some reports in the literature concerning the use of potassium iodide as an adjunct to streptomycin therapy by Woody, Johnson, Avery, and Crowe, Dis. of Chest, 1951, *19*, 373.

We have all been brought up on the idea that syphilitic gummas resolve under treatment with potassium iodide. Jobling and Petersen, J.A.M.A., 1914, *63*, 1930, reported that iodides inactivate antiferment activity of lipoids of tuberculous lesions and thus favor liquefaction of caseous material. However, my belief is that these studies do not establish beyond a doubt whether or not iodides induce the dissolution of fibrous capsules surrounding caseous tissue.

In the July issue of the American Review of Tuberculosis, 1951, there is a report by M. R. Lichtenstein on the use of potassium iodide with para-aminosalicylic acid in chronic fibroid tuberculosis of man. He compares the progress of tuberculosis in some 38 and 27 patients, respectively. The first group received para-aminosalicylic acid, whereas the latter 27 patients received, in addition to the PAS, approximately 1 gram of potassium iodide daily. He observed these patients over a period of 6 to 11 months and found by roentgenographic and bacteriologic examinations that the iodide appeared to have neither a harmful nor a helpful effect on the course of chronic fibroid pulmonary tuberculosis in man.

In my opinion, the information on the subject available in the literature is not very convincing. I feel, therefore, that one should obtain more dependable information on the effect of iodides on already formed fibrous tissue in the lung. This can be accomplished by causing guinea pigs to inhale silica dust or perhaps by intravenous injection of silica dust. Such animals harboring fibrous nodules in their lungs can then be divided into two groups, one receiving iodide and the other group not treated with the salt. It seems to me one

would definitely be able to determine whether iodides really have the purported property of dissolving fibrous tissue.

Another consideration which must be borne in mind is the effect of prolonged use of iodide on thyroid function.

Sincerely yours,
Max B. Lurie (Signed)

MBL:dr

VETERANS ADMINISTRATION
WASHINGTON 25, D. C.

November 30, 1951

DEPARTMENT OF MEDICINE AND SURGERY

IN REPLY REFER TO: 10EE

Dear Dr. Mote:

I have seen carbons of letters written you by Drs. William Tucker and Arthur Walker in answer to your letter of November 21. I feel I can add little or nothing to them. The group at Vanderbilt, I suspect, may have more information pertinent to your question than they have reported on and it might be well to write them. The most complete study that I can remember was at the Oak Terrace Sanatorium in Minnesota, at the time when Dr. Ernest S. Mariette was Medical Director. He has since retired but I believe that Dr. Frank Jennings of the Sunnyside Sanatorium in Indianapolis was present at the time. If I am not mistaken it was published in the American Review in the '30s.

Personally I do not know of any good evidence of any effect, one way or the other, of iodides on tuberculosis. It is true that the older physicians did use iodides as a diagnostic test. If the patient had no sputum, or no tubercle bacilli in the smears of the sputum, the trick was to give iodides until you got both. I sincerely hope you will not bother yourself or embarrass me by sending these idle comments to your consultants. Will be looking forward to seeing you at the St. Louis Conference in January.

Sincerely,
John B. Barnwell (Signed)
John B. Barnwell, M.D.
Chief, Tuberculosis Division

MAYO FOUNDATION
FOR MEDICAL EDUCATION AND RESEARCH
UNIVERSITY OF MINNESOTA GRADUATE SCHOOL
ROCHESTER, MINNESOTA

December 3, 1951

Dear Doctor Mote:

This is in reply to your letter of November 20 concerning possible effects of iodides on the pathogenesis of tuberculosis and the toxic effects of iodides when given clinically.

While I have had some interest in the question of iodine as an antituberculosis agent for many years, we have never explored the problem experimentally. There are, however,

several reports on the effect of iodides in experimental and clinical tuberculosis. In Calmette's book TUBERCLE BACILLUS INFECTION AND TUBERCULOSIS IN MAN AND ANIMALS page 666 you will find a summary of the earlier work up to about 1923.

In my Harben Lectures (London, 1946) you will find a list of various agents studied for possible antituberculosis properties. The information was obtained from the Index Medicus, 1932–1945. Thirty-three reports on iodine are listed. I am sending a reprint of the Harben Lectures which you may find of interest.

For additional information I suggest you communicate with Dr. Arnold Rich, Pathologist, Johns Hopkins Hospital, Baltimore. Have you consulted the book by Wells and Long, THE CHEMISTRY OF TUBERCULOSIS? This is a most comprehensive treatise on the various aspects of the biology of the tubercle bacillus including the chemical aspects of chemotherapy. The authors give a complete review of the various agents and no doubt the iodides are included. Unfortunately, I do not have a copy of this book which was published in 1932.

My own impression regarding the toxicity of iodine is that when used within the usually accepted dose levels and under proper medical supervision to detect possible occurrence of iodism it can be administered with relative safety. Furthermore, I have no evidence that would indicate that iodine under the conditions you mentioned would exert an adverse effect on the pathogenesis of tuberculosis.

In closing I suggest you contact Dr. Esmond Long, one of the authors of the book by Wells and Long mentioned above. He is director of the Phipps Institute, 7th and Lombard Streets, Philadelphia. It is quite likely that he can give you some information regarding the question under consideration.

Sincerely yours,
Wm. H. Feldman (Signed)
William H. Feldman

WHF:lc

STATE OF CONNECTICUT
LAUREL HEIGHTS
STATE TUBERCULOSIS SANATORIUM
SHELTON, CONN.

December 3, 1951

Dear Dr. Mote:

I have your letter of November 20 asking my opinion as to the possible deleterious effects upon active or latent tuberculosis of . . ., a product which contains approximately 100–200 mg. of iodine in the usual daily dose.

I have discussed this question with my colleague, Dr. John O'Connor, and about all either of us can say on this question is, that so far as we know, the situation is just as you have outlined it in your letter. Certainly we know of no definite evidence pro or con on this subject. Since neither of us has ever used iodine preparations in the treatment of tuberculosis, certainly neither of us is qualified to express any opinion which is based on experience. Any opinion which we might express would be so devoid of any adequate basis in actual knowledge that it could not possibly be of any practical value to you.

As you undoubtedly know, a few investigators have, in recent years, explored the possibility of deliberately using potassium iodide along with chemotherapeutic agents in the

treatment of certain types of pulmonary tuberculosis. Such a study has, for example, been carried out by a group at Vanderbilt University in Nashville, Tennessee. You may, therefore, find it worthwhile to address your inquiry to some of the men who have participated in this study. Among these men are Dr. Avery in the Department of Bacteriology at Vanderbilt, Dr. Hollis Johnson whose address is 2122 West End Avenue, Nashville 5, Tennessee, and Dr. Robert A. Goodwin of the Veterans Administration Hospital in Nashville. According to reports which I have heard from this study, no significant difference was observed clinically in the therapeutic results achieved in those patients who received both KI and the chemotherapeutic drugs and those who received the chemotherapeutic drugs alone. I cannot, however, recall the exact doses of KI employed.

I regret to say that this is the only lead I can give you which you might find of some use.

Sincerely yours,
Kirby S. Howlett, Jr. (Signed)
Kirby S. Howlett Jr., M.D.
Assistant Superintendent

KSH:fpm

DR. CARL MUSCHENHEIM
133 EAST SIXTY-FOURTH STREET
NEW YORK 21, N. Y.

December 4, 1951

Dear Dr. Mote,

I apologize for the delay in answering your letter of November 19th. . . . I cannot give you an opinion based on experience with respect to the possible deleterious effect of iodine in tuberculosis, and I have had the same impression as you mention, namely that the belief that it is deleterious is based more on tradition than on demonstrated fact. I have only rarely had occasion to prescribe iodine in patients with active or arrested pulmonary tuberculosis. In these few cases I have observed no deleterious effect.

Very sincerely yours,
Carl Muschenheim (Signed)
Carl Muschenheim, M.D.

CM:AH

BELLEVUE HOSPITAL
CHEST SERVICE
(COLUMBIA UNIVERSITY DIVISION)
27th STREET AND FIRST AVENUE
NEW YORK 16, N. Y.

December 4, 1951

Dear Dr. Mote:

. . . . . .

As to the question of possible effects of iodine in patients with tuberculosis, my own opinion from routine observation from time to time is that no harm is done except possibly when iodism develops. In such instances there may be considerable bronchorrhea which

conceivably might favor a spread of tuberculous pulmonary disease in patients with cavities and positive sputum.

In recent years iodides have been used in combination with streptomycin and other antibiotics and you will find reports from Dr. Kolmer in Philadelphia, and Dr. Goodwin of Nashville. Dr. Goodwin told me recently that he did not observe deleterious effects which he could ascribe to the iodides.

Sincerely yours,
J. Burns Amberson, M.D., (Signed)
Visiting Physician in Charge

THE UNIVERSITY OF CHICAGO
CHICAGO 37, ILLINOIS
DEPARTMENT OF MEDICINE

December 10, 1951

Dear Dr. Mote:

. . . . . I have had no personal experience with iodides in human tuberculosis. The subject is one which has always bothered me and I have never been able to find in the literature any objective evidence that iodides indeed had an unfavorable effect. I am sorry that I cannot give you any more objective opinion than this.

Sincerely yours,
Robert Ebert (Signed)
Robert H. Ebert, M.D.

RHE:ler

DR. JOHN H. SKAVLEM
DR. D. W. HEUSINKVELD
DR. VIRGIL PLESSINGER
UNION CENTRAL LIFE BUILDING
CINCINNATI 2, O.

December 12, 1951

Dear Doctor Mote:

. . . . . Personally I feel that there is no hazard involved with the use of iodine in such doses as contained in this product in cases of pulmonary tuberculosis. We do not hesitate to make injections of lipiodol into the bronchi of cases with pulmonary tuberculosis. I commonly prescribe Syrup Hydriodic Acid in cases of pulmonary tuberculosis with complicating bronchial infection. I do not hesitate to give Lugols Solution in cases of Thyroid disturbance in cases who have pulmonary tuberculosis.

I appreciate your discussion and would like to hear more about the use of the product as it develops.

Sincerely yours,
John H. Skavlem (Signed)
John H. Skavlem, M.D.

JHS:mw

UNIVERSITY OF COLORADO
DEPARTMENT OF MEDICINE
4200 EAST NINTH AVENUE
DENVER 7, COLORADO
February 8, 1952

Dear Dr. Mote:

. . . . . .

When I first started in practice with Dr. S. G. Bonney in 1914, I found that he used very frequently Gardner's syrup of hydriotic acid, one teaspoon in a glass of water three times after meals for the very irritable non-productive cough during the early stages of acute tuberculous infection. Neither he nor I over the years ever saw any harm from it.

You are, of course, thoroughly familiar with Petersen's and Jobling's experimental work suggesting that the iodides might interfere with anti-enzymes and thus encourage the breakdown of tuberculous lesions. We have during the past years had a grant-in-aid from the National Tuberculosis Association to study the effect of the combined use of streptomycin and potassium iodide in experimental tuberculosis. This work is not ready for publication, but will be ready this spring. It was done by Dr. Mary Alice Hamilton* at the Colorado Foundation for Research in Tuberculosis Laboratory in Colorado Springs. I am Director of the Foundation. Very briefly, she found the following:

1. Guinea pigs infected with a virulent tubercle bacillus and given iodides developed rapidly a progressive tuberculosis. A number of the animals developed tuberculous meningitis and central nervous system lesions.
2. Guinea pigs infected with virulent tubercle bacillus and given iodides and streptomycin also did badly, but not as badly as the first group. Some of the animals did develop tuberculous meningitis, but not as many.
3. Animals were first vaccinated with BCG and later infected with a virulent organism and then given streptomycin and potassium iodide. They did better than the same animals that were treated with streptomycin alone.

All of this would suggest that in a chronic form of tuberculosis, the combined use of streptomycin and potassium iodide might be more helpful than streptomycin alone, but that it is dangerous to use potassium iodide in acute tuberculous infections.

. . . . . .

You are doubtless aware that Lipiodol is not infrequently used in tuberculous patients, first, where the diagnosis might be in doubt but tuberculosis is ultimately proved; and second, in patients well-known to have tuberculosis but where a bronchogram is essential to accurate interpretation of the pulmonary pathology. I have always been reluctant to use Lipiodol in a frankly tuberculous patient for two reasons: first, because of the retention of Lipiodol in the lung, so to speak "muddying" the radiologic picture and making later interpretation for some weeks, if not months, somewhat difficult. Also, I have been fearful that the iodine released by the Lipiodol might aggravate the pulmonary tuberculosis. I realize, of course, how difficult it must be to be sure whether the disease is aggravated or not aggravated, but I must admit that I never have seen a case where Lipiodol had aggravated a tuberculous process.

Please forgive me for my delay in answering your letter. With all good wishes,

Sincerely yours,
James J. Waring (Signed)
James J. Waring, M.D.
Professor of Medicine

JJW:mls

* The study referred to is published in this issue of the REVIEW on page 680. [Editor]

OFFICE OF THE CHIEF OF MEDICAL SERVICE
FITZSIMONS GENERAL HOSPITAL
DENVER 8, COLORADO

IN REPLY
REFER TO: MEDEO-M

ADDRESS REPLY TO
COMMANDING GENERAL
NOT TO INDIVIDUALS

12 February 1952

Dear Dr. Mote:

I received your letter recently concerning the use of "iodides" in tuberculosis. I have had no research experience regarding the effect of iodides in tuberculosis. I really have no comments to make on the subject. Like everyone else, I have always felt that iodides were contraindicated in tuberculosis and I would welcome any scientific facts that would further clarify this point. We have seen no serious ill effects from the lipiodol in diagnostic studies performed on patients with tuberculosis but I have made no special study of this matter. We seldom order bronchograms in tuberculosis because of the retention of dye obscuring the roentgen findings in comparison of films.

I welcome any information you can give me on this subject.

Sincerely,
Carl W. Tempel (Signed)
Carl W. Tempel
Colonel, MC
Chief of Medical Service

CWT/mi

BAYLOR UNIVERSITY
College of Medicine
Houston 5, Texas

March 10, 1952

Department of
Internal Medicine

Dear Doctor Mote:

Please pardon my long delay in replying to your inquiry as to my opinion on the effect of iodides in tuberculosis. I hope that this reply is not too late to be of use to you.

This question is one which is certainly of interest to physicians who see much of tuberculosis. Part of my delay in replying to you was the result of an attempt on my part to cover some case material which, unfortunately, I have not been able to do. I can only quote you from memory the circumstances surrounding these two cases.

The first case was a white male in the middle decades of life who had a moderately advanced pulmonary tuberculosis which was questionably active. Iodides in rather large doses were given to him for some other condition, the exact nature of which I cannot remember, and this patient was subsequently observed to have a spread of his tuberculosis on about the second month of iodide treatment.

The other case was seen at the University of Michigan Hospital. This was a patient who was believed to have a fungus infection and was treated with large doses of iodides.

Subsequent to such treatment the fungus disease was seen to spread in a disseminated fashion throughout the body. The patient died and the autopsy revealed a disseminated miliary tuberculosis.

I hope that you are aware of some work carried on by Dr. Mary Alice Hamilton at the Foundation for Research in Tuberculosis in Colorado Springs, Colorado. Dr. Hamilton has done fairly extensive work using potassium iodide and watching the influence of this drug on the course of experimental tuberculosis in the guinea pig. . . . . I certainly would advise that you contact her. I am indeed apologetic that I cannot give you a more authoritative opinion on this interesting subject. As a matter of practice I do not give iodides to patients with tuberculosis.

Again please pardon my delay and I hope that this information is of some value to you.

Sincerely yours,
/Signed/
Daniel E. Jenkins, M.D.
Associate Professor of Medicine

DEJ:mh
COPY:MEM

LUNG IMMOBILIZER THERAPY IN PULMONARY TUBERCULOSIS

To the Editor of the American Review of Tuberculosis:

Since Hemphill, Owen, and Steele, in their study, "Lung Immobilizer Therapy in Pulmonary Tuberculosis: A Clinical Study" (Am. Rev. Tuberc., 1952, *66*, 261) did not use our method of immobilizing lung therapy, a valid comparison of their results with those of my colleagues and myself is unjustified. I am chiefly concerned that the readers of this journal be misled into believing that their regimen was an adequate substitute for the use of the immobilizing lung chamber as actually described in the papers (1, 2, 4, 5, 6, 7, 9, 10)[1] from which they have appeared to quote but which, in fact, they have critically misrepresented.

On page 2 of their paper, the following statement is made:

> "Inasmuch as marked improvement (5, 6) had been reported in patients treated three and one-half to four months for six to eight hours a day, it was decided, since the present investigators had only one chamber available, that the patients would be treated for eight hours a day."

We had never advocated chamber therapy for six to eight hours daily, nor two periods of four hours each, nor permitted patients their previous ambulatory activity when outside the chamber. Our results were based on consecutive treatment during the day from breakfast to a time shortly before retiring; the only exceptions were (*a*) one patient in whom closure of cavity and negative sputum took place on eight hours' chamber therapy daily; this patient had a special nurse to enforce strict bed rest the remainder of the day; (*b*) the first case ever treated, in which the chamber was cautiously tried for six hours daily. This patient was admittedly a *"partially treated patient"* in whom the equalizing pressure used *"may not have been adequate to arrest lung movement completely"* (5).

The statement of Hemphill *et al.* should be compared to the actual content of the papers which they gave as references.

> *"In the others (except for the first case treated) the patient was in the chamber from 9:00 a.m. to 12 noon. He was taken out for lunch and dinner, generally also for milk and orange juice at 4:00 p.m. At 10:00 p.m. he was removed to his bed and soon went to sleep. If he was unable to sleep easily, a capsule of Nembutal or Sodium Amytal was prescribed. He was thus exposed to lung rest for twelve to thirteen hours daily . . . no physical examination was permitted except the one on admission and departure."* (5)

> *"Although ten hours a day of residence in the chamber is considered the optimum time, recovery took place in one patient following a course of eight hours a day for three months. However, one patient, who had a large cavity in the left upper lobe, was treated for five hours a day, in an experimental trial of the duration of treatment, without a favorable result. A succeeding trial of ten hours a day was followed by closure of cavity with the development of negative sputum in a period of four months."* (9)

> *"With our present plan of treatment, each machine is operated on two shifts of ten hours each."* (4)

> *"The patient who has had good supervision and training during the first ten days generally manifests no sign of breathing during the remainder of treatment, not less than ten hours a day for four to five months."* (10)

> *"The duration of treatment is the major part of the day, such as from 9 to 1 in the morning, 2 to 6 in the afternoon and 7 to 9:30 in the evening. In the patients who responded favorably, 8 to 11 hours a day of immobilizing lung therapy has been used."* (6)

[1] The reference numbers apply to the bibliography of the paper, "Lung immobilizer therapy in pulmonary tuberculosis," by Hemphill *et al.*

The opening sentence of the Hemphill *et al.* paper, page 1, contains the following misleading statement:

"In 1940 Barach (1, 2) applied the principle of Thunberg's barospirator (3) to the treatment of tuberculosis."

In 1940 I reported experiments which indicated that ventilation achieved by the barospirator principle did *not* result in continued arrest of chest movement (1, 2). In fact, in these papers the following statements appear:

"In the studies of Thunberg (1) it is stated that a difference in pressure probably arises between the air contained in the chamber atmosphere and that contained in the lungs, a difference as great as that occurring in normal respiration, namely, 2 or 3 mm. Hg. Enghoff (2) admitted that the small differences in pressure between the chamber air and the air in the lung entails another assumption, namely, a slight compression of the thoracic walls in the positive phase and a slight expansion in the negative phase." (1)

"It was shown that patients with pulmonary disease treated in a chamber by an alternating pressure of +55 mm. Hg, 25 times a minute as originally suggested by Thunberg (7) for respiratory paralysis, were unable to maintain continuous arrest of lung movement, and, furthermore, that compression and expansion of the chest resulted from the positive and negative cycle of pressure respectively." (2)

The principles and methods of equalizing the pressure applied to the chest and diaphragm were described in our studies in 1940. It is, therefore, misleading for Hemphill *et al.* to state that: "Barach (1, 2) applied the principle of Thunberg's barospirator (3) to the treatment of tuberculosis," as well as to refer to the development of equalizing the chest pressures to the study of Grosfeld and Nash (4).

The heart of the matter is, not only that we did not report "marked improvement" in patients treated "for six to eight hours a day," nor that we used longer consecutive hours of treatment, but that our regimen outside the chamber could not be compared to that described by Hemphill *et al.* No physical examination except the one on admission and departure was permitted in our program which was dedicated to obtaining the maximum body and lung rest feasible, during and after chamber therapy. Maximal breathing capacity tests were considered hazardous for months after sputum had become negative.

Hemphill *et al.* state that the criteria set up in their study "were considered to offer an objective standard for measuring the merits of this type of treatment" but it was clear to the writer that their investigation was not designed to test the validity of immobilizing lung chamber therapy according to our regimen but for a scientific objective of their own. During the visit in which I was accorded the privilege of seeing their study in progress, I was told that patients were allowed, as stated in their paper, "the same amount of activity as during the observation period." Walking along the corridor to the chamber or elsewhere was permitted, as during the time prior to chamber therapy for control purposes.

When I tried the first case of pulmonary tuberculosis in the chamber for six hours daily, I was worried by a number of contingencies, such as atrophy of chest musculature, spread of disease, and increased nerve tension. Fortunately, since we did not observe these adverse effects of properly managed treatment (from 1938 on), we did not make the mistake of trying short or divided daily periods of residence in the chamber, but rather posed the question: *"Since ten hours a day accomplishes cavity closure, and five hours a day appeared too little, should twelve to eighteen hours be tried?"* (7) Nor does the fact that Hemphill *et al.* said they had only one chamber available seem an adequate reason for limiting the duration of daily treatment, especially since our results were based on such a different regimen which, as noted above, included a longer duration of daily treatment.

In a spirit of fair criticism, the writer believes that the findings of Hemphill *et al.* cannot with justice be considered comparable to those reported by my colleagues and myself, in respect to the clinical value of immobilizing lung chamber therapy in patients with chronic pulmonary tuberculosis.

PRESBYTERIAN HOSPITAL
NEW YORK NEW YORK

ALVAN L. BARACH

September 29, 1952

References from "Lung Immobilizer Therapy in Pulmonary Tuberculosis. A Clinical Study" by Roger A. Hemphill, George C. Owen, and John D. Steele, Am. Rev. Tuberc., 1952, 66: 261

(1) BARACH, A. L.: The treatment of advanced pulmonary tuberculosis by continuous arrest of lung movement produced by residence in an equalizing alternating pressure chamber, Tr. A. Am. Physicians, 1940, *55*, 98.

(2) BARACH, A. L.: Immobilization of lungs through pressure, Am. Rev. Tuberc., 1940, *42*, 586.

(3) THUNBERG, T.: The barospirator: A new machine for producing artificial respiration, Skandinav. Arch. f. Physiol., 1926, *48*, 80.

(4) GROSFELD, W., AND NASH, J. C.: Lung immobilization chamber therapy in chronic pulmonary tuberculosis, Dis. of Chest, 1952, *21*, 296.

(5) BARACH, A. L.: Continuous arrest of lung movement, Am. Rev. Tuberc., 1941, *43*, 56.

(6) BARACH, A. L.: Continuous immobilization of the lungs by residence in the equalizing pressure chamber in the treatment of pulmonary tuberculosis, Dis. of Chest, 1946, *12*, 521.

(7) BARACH, A. L., EASTLAKE, C., JR., CULLEN, J. H., AND HERBEN, G. F.: Closure of tuberculous cavities, J.A.M.A., 1949, *139*, 833.

(8) AMERICAN TRUDEAU SOCIETY: Report of Clinical Subcommittee of the Committee on Research and Therapy on "Iron Lung" treatment, Bulletin, National Tuberculosis Association, February, 1949, p. 28.

(9) CULLEN, J. H., MYERS, R. K., BARACH, A. L., AND HERBEN, G. F.: Closure of cavities in pulmonary tuberculosis produced by immobilization of both lungs, Dis. of Chest, 1948, *14*, 345.

(10) BARACH, A. L., EASTLAKE, C., JR., AND BECK, G. J.: Clinical results and physiological effects of immobilizing lung chamber therapy in chronic pulmonary tuberculosis, Dis. of Chest, 1951, *20*, 160.

(11) BARACH, A. L., AND BROOKS, J. W.: Physiological therapy in diseases of the respiratory system, Bull. U. S. Army M. Dept., 1948, *8*, 524.

NOTES

ANNUAL MEETING OF THE AMERICAN TRUDEAU SOCIETY—1953

The American Trudeau Society, medical section of the National Tuberculosis Association, invites the submission of abstracts of scientific papers for presentation at its next annual meeting in Los Angeles, California, May 18 to 22, 1953, at the Hotel Biltmore.

Full information can be obtained by writing to the Chairman of the Medical Sessions Committee, American Trudeau Society, 1790 Broadway, New York 19, N. Y.

ANNUAL MEETING OF THE AMERICAN ACADEMY OF TUBERCULOSIS PHYSICIANS—1953

The American Academy of Tuberculosis Physicians will hold its annual meeting in New York City, Hotel Roosevelt, May 30, 1953. Requests for program space, complete with title and abstract, should be sent to Dr. O. S. Levin, P. O. Box 7011, Denver 6, Colorado, at the earliest possible date.

COURSES IN LABORATORY DIAGNOSIS OF TUBERCULOSIS

In cooperation with the Division of Chronic Disease and Tuberculosis, Public Health Service, the Bacteriology Laboratories of the Communicable Disease Center, Chamblee, Georgia, will offer two courses in the laboratory diagnosis of tuberculosis on the following dates:

March 16–27, 1953
November 16–27, 1953

The courses are open to all grades of employed laboratory personnel who are approved by their State Health Officers. Practical laboratory training in all phases of tuberculosis bacteriology, including preparation of culture media, microscopy, cultural procedures, diagnostic use of animals, and testing of drug sensitivity, will be included in the course. No tuition or laboratory fees are charged. Reservations for the courses should be made well in advance.

In addition, two similar courses will be given for laboratory directors, senior laboratory staff members, physicians, and others of comparable professional standing on the following dates:

March 30–April 3, 1953
November 9–13, 1953

Additional information and applications may be obtained from Laboratory Training Services, Communicable Disease Center, Public Health Service, P. O. Box 185, Chamblee, Georgia.

119th MEETING OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Saturday Afternoon, December 27, 1952

2:00 p.m., Kiel Assembly Hall 3, *Symposium: Chemotherapy of Tuberculosis*
(Arranged by Dr. Alfred Goldman, Washington University, School of Medicine)
Alfred Goldman, *Presiding:*

1. Antimicrobial Therapy of Pulmonary Tuberculosis, FORREST W. PITTS, Capt., M.C., U.S.A., and CARL W. TEMPLE, Colonel, M.C., U.S.A., Fitzsimons Army Hospital, Denver, Colorado.

2. The Laboratory Evaluation of the Anti-tubercular Activity of the Hydrazine Derivatives of Isonicotinic Acid, E. GRUNBERG, Hoffman-La Roche, Inc., Nutley, N. J.; Department of Health, Newark, Newark, N. J.
3. The Acute Pharmacology in Man of the INAH Compounds, CARL C. PFEIFFER, University of Illinois, School of Medicine, Chicago, Illinois.
4. Use of Isoniazid and Iproniazid Compounds in Clinical Tuberculosis, M. R. LICHTENSTEIN, University of Illinois, School of Medicine; and Municipal Tuberculosis Sanitarium of Chicago, Illinois.

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• *Complete information about these and other Fairchild x-ray units and accessories, such as roll-film developing units, all of which are available from your x-ray equipment supplier, can be obtained by writing to* Fairchild Camera and Instrument Corporation, 88-06 Van Wyck Boulevard, Jamaica 1, New York, Department 160-28C.

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